Received:
19 February 2020

Revised:
25 May 2020

Accepted:
06 July 2020

<https://doi.org/10.1259/bjr.20200159>

Cite this article as:

Sawada M, Kunieda E, Akiba T, Kabuki S, Nagao R, Fukuzawa T, et al. Dosimetric study of whole-brain irradiation with high-energy photon beams for dose reduction to the scalp. *Br J Radiol* 2020; **93**: 20200159.

FULL PAPER

Dosimetric study of whole-brain irradiation with high-energy photon beams for dose reduction to the scalp

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Objective: To evaluate the efficiency of high-energy photons for mitigating alopecia due to whole-brain irradiation (WBRT).

Methods: Planning CT data from 10 patients who received WBRT were collected. We prepared 4 WBRT plans that used 6 or 15 MV photon beams, with or without use of a field-in-field (FiF) technique, and compared outcomes using a treatment planning system. The primary outcome was dose parameters to the scalp, including the mean dose, maximum dose, and dose received to 50% scalp (D50%). Secondary outcomes were minimum dose to the brain surface.

Results: Using FiF, the mean doses were 24.4–26.0 and 22.4–24.1 Gy, and the maximum doses were 30.5–32.1 and 28.5–30.8 Gy for 6 and 15 MV photon beams, respectively.

Without FiF, the mean doses were 24.6–26.9 and 22.6–24.5 Gy, and the maximum doses were 30.8–34.6 and 28.6–32.4 Gy for 6 and 15 MV photon beams. The 15 MV plan resulted in a lower scalp dose for each dose parameter ($p < 0.001$). Using FiF, the minimum doses to the brain surface for the 6 and 15 MV plans were 28.9 ± 0.440 and 29.0 ± 0.557 Gy, respectively ($p = 0.70$). Without FiF, the minimum doses to the brain surface for the 6 and 15 MV plans were 28.9 ± 0.456 and 29.0 ± 0.529 , respectively ($p = 0.66$).

Conclusion: Compared with the 6 MV plan, the 15 MV plan achieved a lower scalp dose without impairing the brain surface dose.

Advances in knowledge: High-energy photon WBRT may mitigate alopecia of patients who receiving WBRT.

INTRODUCTION

Brain metastases from cancer are common, occurring in 8–10% of cancer patients^{1,2} and 16–26% of autopsy cases.^{3–5} It is believed that 32–53% of patients with brain metastases have a single metastasis.^{4–7} Surgery is indicated in patients with a small number of metastases, and patients in whom brain metastatic lesion resection is successful can expect to have a relatively good prognosis. Various novel systemic treatments, including target therapies and immunotherapy, have recently been developed; however, these agents are often ineffective for treatment of brain metastases due to the blood–brain barrier. Radiation therapy plays an important role in brain metastasis treatment regardless of the number of tumors or prognosis. Radiation therapy for brain metastasis consists of whole-brain radiation therapy (WBRT) as well as local irradiation therapies, such as stereotactic radiotherapy or radiosurgery. Although stereotactic radiotherapy has a tremendous impact on brain metastasis control, WBRT remains an important option for patients with multiple metastases or disseminated disease,

as recommended in the National Comprehensive Cancer Network guidelines.⁸ Moreover, WBRT is indicated in patients with acute lymphoblastic leukemia and small cell lung cancer for prophylaxis of brain metastases, as well as for treatment of primary central nervous system (CNS) lymphoma.

Alopecia almost always inevitably occurs in patients who undergo WBRT. Patients requiring WBRT frequently have a poor prognosis and are in the palliative stage of treatment, so alopecia at this time is often a substantial problem for these patients, both physically and mentally. Recently, attempts have been made to reduce radiation doses to the scalp and to mitigate alopecia with modern techniques such as intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT).^{9–15} However, the two lateral-opposed field technique with 4–8 MV photon beams remains as the standard method for WBRT for brain metastases.

High-energy photons have greater build-up effects, therefore providing lower absorbed doses at the surface and less attenuation in deep tissue compared with lower-energy photons. We estimate that high-energy photons may spare the scalp and mitigate alopecia, and provide less attenuation in the brain. Therefore, when opposite beams are employed, inhomogeneity due to differences in thickness may be reduced, even when a field-in-field (FiF) method is performed. However, a greater build-up effect may also spare the surface of the brain; hence, it is necessary to confirm the appropriate dose to be delivered. The present study is a dosimetric study comparing WBRT with high- and low-energy beams using a treatment planning system.

METHODS AND MATERIALS

Patients and simulation

Data from 10 patients >20 years old who were clinically diagnosed with metastatic brain tumors and had previously undergone WBRT at Tokai University Hospital between August 2018 and December 2018 were collected. Patients who had undergone intracranial surgery were excluded. This study assessed only physical dose distributions; therefore, a small number of patients was considered sufficient.

We used simulation CT images of treated patients obtained by SOMATOM Definition AS (Siemens Healthineers, Munich, Germany). CT images were acquired with a 3 mm slice thickness, thermoplastic mask immobilization, and no contrast material. The Eclipse treatment planning system (Varian Medical System, Palo Alto, CA) was used for contouring and dose calculations.

Contouring

The clinical target volume was defined as the whole brain (to inner surface of the skull and foramen magnum), and expanded 5 mm in all directions for the planning target volume (PTV). The depth of the hair follicle from the skin surface is believed to be at 3.5–4.2 mm.^{16–20} Therefore, we defined the “scalp”, the organ-at-risk, as the region extending to a 5 mm depth from the skin surface for dose assessment in this study. The scalp was divided into four subvolumes (superior third of the whole scalp and

anterior, middle, and posterior thirds of the inferior two-thirds of the scalp). Regions caudal from the upper edge of the orbit and caudal from the base of the auricular area were excluded from the anterior and middle subvolumes of the scalp for assessment, respectively (Figure 1).

The brain surface was defined as a 3 mm depth from the surface of brain parenchyma as observed on CT.

Treatment planning and dose calculation

Two opposed lateral 6 or 15 MV photon beams with the gantry tilted a few degrees for lens-sparing were used for WBRT planning. Superior, anterior, and posterior borders of portals were ≥ 2 cm from the outside of the body. The inferior border was 5 mm outside the PTV and C1-2 intervertebral space (Figure 2). The prescribed dose was 30 Gy (10 fractions) to the prescription point, which is the center of gravity of the PTV. The analytical anisotropic algorithm (AAA) in the Eclipse treatment planning system was used for dose calculation. If FiF was used, 2–4 subfields were used to reduce the maximum dose to 107% of the prescribed dose. Four plans (6 MV with FiF, 6 MV without FiF, 15 MV with FiF, and 15 MV without FiF) were created from one simulation CT.

Statistical analysis

The primary outcome was the dose parameters to the scalp, *i.e.* mean dose, maximum dose, and the lowest dose received by 50% of the target volume ($D_{50\%}$), per subvolume. The secondary outcome was the minimum dose of the brain surface and the homogeneity index of the CTV. The homogeneity index was defined as $(D_{2\%} - D_{98\%}) / D_{50\%}$, where $D_{2\%}$, $D_{98\%}$ and $D_{50\%}$ are the lowest doses received by 2, 98 and 50% of the CTV. The mean of these parameters for the 6 and 15 MV plans was compared by paired *t*-test, with or without FiF.

RESULTS

The mean scalp doses with FiF for each subvolume are shown in Table 1. Compared with 6 MV plans, 15 MV plans lowered

Figure 1. Subvolumes of the scalp for dose assessment. The scalp was divided into four subvolumes; superior (yellow), anterior (blue), middle (green) and posterior (red). Superior refers to the superior third of the whole scalp. Anterior refers to the anterior third of the inferior scalp, in which the inferior border was defined as the top of the orbit. Middle refers to the middle third of the inferior scalp, in which inferior border was defined as the top of the ear. Posterior refers to the posterior third of the inferior scalp, in which the inferior border was defined as the foramen magnum. A: cranial view; B: frontal view; C: lateral view

Figure 2. WBRT treatment plan. Two opposed lateral beams with gantry tilting for lens-sparing. A: axial view; B: beam's eye view. Blue: right eye lens; green: left eye lens. WBRT, whole-brain irradiation.

the mean dose, maximum dose, and D50% significantly by 1.8–2.0 Gy, 0.5–2.0 Gy, and 7.7–8.0 Gy, respectively.

The mean scalp doses without FiF for each subvolume are shown in Table 2. Compared with 6 MV plans, 15 MV plans lowered the mean dose, maximum dose, and D50% significantly by 2.1–2.8 Gy, 2.2–3.6 Gy, and 7.6–10.5 Gy, respectively.

The mean minimum dose to the brain surface with FiF was 28.87 Gy (± 0.44) for 6 MV plans and 28.98 Gy (± 0.56) for 15 MV plans, with no significant difference ($p = 0.701$) (Table 3). The minimum dose in 2 of 10 patients for both the 6 and 15 MV plans was <95% of the prescribed dose. The mean minimum dose to the brain surface without FiF was 28.87 Gy (± 0.46) for 6 MV plans and 28.99 Gy (± 0.66) in 15 MV plans, with no significant difference ($p = 0.663$) (Table 3). The minimum dose in 3 of 10 patients for the 6 MV plan and 2 of 10 patients for the 15 MV was <95% of the prescribed dose.

The homogeneity index with FiF was 0.057 (± 0.007) for 6 MV plans and 0.053 (± 0.005) for 15 MV plans, and tended to be lower for 15 MV plans, although not to a statistically significant degree ($p = 0.065$). The homogeneity index without FiF was 0.099 (± 0.011) for 6 MV plans and 0.077 (± 0.005) for 15 MV plans, being significantly lower for 15 MV plans ($p < 0.001$) (Table 4).

The data from each patient are provided in the [Supplementary Material 1](#).

DISCUSSION

This study demonstrated the efficacy of high-energy photons in lowering the scalp dose significantly in WBRT. High-energy photons provided a sufficient dose to the brain parenchyma and a homogenous dose distribution.

Photon beams of 4–8 MV are often used in head-and-neck or cranial irradiation to avoid dose reduction to the surface caused by build-up effects. For the same reason, WBRT tends to be performed using relatively lower-energy beams. High-energy beams (>10 MV) may produce neutrons, even though they have little effect on patients or technologists; therefore, they tend to be avoided for newly installed machines.^{21,22} However, high-energy beams are advantageous in terms of skin-sparing effect, homogeneity and attenuation when parallel-opposite beams were used. With the recent widespread adoption of IMRT and VMAT, high-energy photon beams are being used less frequently. Nevertheless, the use of 10 MV photon beams is common and 15 MV beams are still used worldwide. Although 15 and 6 MV beams were compared in this study because of their availability in Tokai University Hospital, some studies using beams of other energies, such as 10 MV, should be performed for further evaluation.

Table 1. Dose parameter of scalp with FiF

Subvolumes	Mean dose (Gy)		Maximum dose (Gy)		D50% (Gy)	
	6 MV (SD)	15 MV (SD)	6 MV (SD)	15 MV (SD)	6 MV (SD)	15 MV (SD)
Superior	24.4 (2.2)	22.4 (2.0)	31.6 (0.4)	30.5 (0.5)	26.5 (1.2)	24.1 (1.1)
Anterior	24.5 (1.3)	22.5 (1.2)	30.5 (0.7)	28.5 (1.0)	25.8 (0.8)	23.6 (0.6)
Middle	26.0 (1.4)	24.0 (1.3)	31.8 (0.1)	30.8 (0.3)	27.4 (1.0)	25.0 (0.8)
Posterior	26.0 (1.2)	24.2 (1.1)	32.1 (0.1)	31.6 (0.2)	27.7 (0.9)	25.4 (0.9)

D50%, the least dose received by 50% of the target volume; FiF, field-in-field.

$p < 0.001$ for all parameters and all subvolumes.

Table 2. Dose parameter of scalp without FiF

	Mean dose (Gy)		Maximum dose (Gy)		D50% (Gy)	
	6 MV (SD)	15 MV (SD)	6 MV (SD)	15 MV (SD)	6 MV (SD)	15 MV (SD)
Subvolumes						
Superior	25.8 (2.3)	23.0 (2.1)	34.1 (0.6)	31.7 (0.8)	27.8 (1.2)	24.7 (1.1)
Anterior	24.6 (1.3)	22.6 (1.2)	30.8 (0.7)	28.6 (1.0)	25.9 (0.8)	23.6 (0.6)
Middle	26.2 (1.4)	24.0 (1.3)	34.6 (0.5)	31.0 (0.5)	27.6 (1.1)	25.0 (0.8)
Posterior	26.9 (1.2)	24.5 (1.2)	34.6 (0.3)	32.4 (0.3)	28.5 (0.9)	25.7 (0.8)

D50%, the least dose received by 50% of the target volume ; FiF, field-in-field.

$p < 0.001$ for all parameters and all subvolumes.

The results of this study revealed that WBRT with 15 MV beams achieves a reduced scalp dose but an effective sufficient brain surface dose. To our knowledge, this is the first study to assess the efficacy of high-energy photons in WBRT. We suggest that the vertex area where beams are incident at a near-horizontal angle might be less susceptible to dose reduction effects of build-up than the lateral area where beams are incident at a vertical angle. However, the scalp dose was reduced at the vertex area, as with the other subvolumes. This suggests that high-energy photons may also provide scalp dose reduction for IMRT and/or VMAT with little impact of any build-up effect when using beams from multiple directions.

Radiation-induced alopecia is caused by radiation exposure to the hair follicle. However, the definition of hair follicle areas is generally not established on planning CT. Several dermatological studies reported that the depth of hair follicles from the skin surface is 3.5–4.2 mm.^{16–20} The definition of the scalp region has varied among previous hair-sparing IMRT/VMAT studies, including 3 mm from the skin and 5 mm from the skull in patient CT. Some studies used phantom and dosimeter as a substitute for the actual patient.^{9–12} In contrast, two studies defined the scalp region as 5 mm from the skin surface,^{9,14} which also includes the depth of hair follicles, which is consistent with the abovementioned dermatological studies. Therefore, we used this definition for comparison.

Several previous studies showed dose reductions in the shallow depth of the scalp with use of IMRT or VMAT at energies <10 MV, thus avoiding neutron contamination.^{21,22} However, presently, WBRT is mostly performed using conventional techniques, which are preferable in terms of cost efficiency. In addition, in some countries, such as Japan, use of IMRT for WBRT is very restricted and not covered by insurance. Therefore, we did not conduct dosimetric comparisons between our method and IMRT. We could not directly compare our results with those of previous studies because of the different assessment methods used.^{9–15} One of those studies, in which the scalp was defined as

the region spanning from the skin surface to a 5 mm depth, as in our study, reported mean and maximum doses to the scalp of 22.43 and 33.84 Gy, respectively, for 3D conventional radiotherapy (3D-CRT) and 16.33 and 32.95 Gy, respectively, for IMRT.¹⁴ In the present study, the mean and maximum doses to the scalp for 15 MV WBRT were 22.4–24.1 Gy and 28.5–31.6 Gy, respectively. Whereas the mean dose to the scalp was not reduced by 15 MV WBRT compared with IMRT, the maximum dose was reduced to the same extent as IMRT. This might suggest that the dose-reduction effect of IMRT is stronger in the low to middle dose region of the scalp near the surface but weaker in the deep high-dose region, where hair follicles exist. Further clinical trials verifying the differences in dose distribution to the scalp and clinical benefits between 3D-CRT and IMRT/VMAT are needed.

Although IMRT or VMAT may have dosimetric advantages over 3D-CRT in terms of scalp sparing, 3D-CRT is still an essential option for treating brain metastases for the following reasons. First, IMRT or VMAT is not yet widespread; in Japan, 498 of 717 institutions do not perform IMRT.²³ Metastatic brain tumors are common for cancer patients,^{1,2} so WBRT is not only performed in high volume centers which can perform IMRT. Second, IMRT or VMAT can result in a longer time until treatment initiation compared with 3D-CRT. In recent clinical trials, 51–59% of patients receiving WBRT had neurological symptoms,^{24,25} which is considered to be more common in real world. Patients with symptomatic brain metastases may require urgent treatment. The technique used in the present study is superior to IMRT or VMAT in that it can be performed widely and initiated quickly

Previous studies report that the threshold dose to the scalp for Grade 1 or higher permanent alopecia is 30 Gy irradiation, and the dose for Grade 3 or higher alopecia in 50% of cases is 46 Gy irradiation.^{26,27} Other studies have suggested that temporal alopecia is initiated by absorbed doses as low as 2 Gy.^{28,29} Recent

Table 3. Minimum dose to the brain surface

	6 MV (SD)	15 MV (SD)	<i>p</i> -value
FiF	28.9 (0.4)	29.0 (0.6)	$p = 0.701$
No FiF	28.9 (0.5)	29.0 (0.5)	$p = 0.663$

FiF, field-in-field.

Table 4. Homogeneity index of the brain

	6 MV (SD)	15 MV (SD)	<i>p</i> value
FiF	0.057 (0.007)	0.053 (0.005)	$p = 0.065$
No FiF	0.098 (0.011)	0.077 (0.009)	$p < 0.001$

FiF, field-in-field.

Homogeneity index = (D2%-D98%)/D50.

D_{2%}, D_{98%} and D_{50%} are the least doses received by 2%, 98 and 50% of the CTV.

normal tissue complication probability models for temporal alopecia suggested that the probability of alopecia is dose-dependent with no clear threshold.^{30,31} In the present study, the scalp mean and maximum doses provided by 15 MV WBRT were 22.4–24.1 and 28.5–31.6 Gy, respectively, which were 0.5–2 Gy lowered compared with the doses provided by 6 MV WBRT. This suggests that 15 MV WBRT cannot prevent temporal alopecia completely but may lower its occurrence compared with 6 MV WBRT.

Limitations of this study include comparing radiation doses only using a treatment planning system. Dose calculations of treatment planning systems at build-up regions such as the scalp surface are known to be uncertain.³² It is also unclear how much

this dose reduction of the scalp mitigates alopecia and improves patient quality of life. Further clinical studies assessing the benefit of this technique in real patients are needed.

CONCLUSION

15 MV photon WBRT provides lower scalp doses without significant dose reduction to the brain surface independent of the presence of FiF technique on a treatment planning system. Further Phase II studies assessing real-world clinical benefit are needed to confirm the utility of this strategy.

ACKNOWLEDGMENT

This work was partially supported by JSPS KAKENHI Grant Number 20K08034.

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