Dosimetric analysis of the alopecia preventing effect of hippocampus sparing whole brain radiation therapy

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Abstract

Background: Whole brain radiation therapy (WBRT) is widely used for the treatment of brain metastases. Cognitive decline and alopecia are recognized adverse effects of WBRT. Recently hippocampus sparing whole brain radiation therapy (HS-WBRT) has been shown to reduce the incidence of memory loss. In this study, we found that multi-field intensity modulated radiation therapy (IMRT), with strict constraints to the brain parenchyma and to the hippocampus, reduces follicular scalp dose and prevents alopecia.

Methods: Suitable patients befitting the inclusion criteria of the RTOG 0933 trial received Hippocampus sparing whole brain radiation. On follow up, they were noticed to have full scalp hair preservation. 5 mm thickness of follicle bearing scalp in the radiation field was outlined in the planning CT scans. Conventional opposed lateral WBRT radiation fields were applied to these patient-specific image sets and planned with the same nominal dose of 30 Gy in 10 fractions. The mean and maximum dose to follicle bearing skin and Dose Volume Histogram (DVH) data were analyzed for conventional and HS-WBRT. Paired t-test was used to compare the means.

Results: All six patients had fully preserved scalp hair and remained clinically cognitively intact 1–3 months after HS-WBRT. Compared to conventional WBRT, in addition to the intended sparing of the Hippocampus, HS-WBRT delivered significantly lower mean dose (22.42 cGy vs. 16.33 cGy, \( p < 0.0001 \)), \( V_{24} \) (9 cc vs. 44 cc, \( p < 0.0000 \)) and \( V_{30} \) (9 cc vs. 0.096 cc, \( p = 0.0106 \)) to follicle hair bearing scalp and prevented alopecia. There were no recurrences in the Hippocampus area.

Conclusions: HS-WBRT, with an 11-field set up as described, while attempting to conserve hippocampus radiation and maintain radiation dose to brain inadvertently spares follicle-bearing scalp and prevents alopecia.

Keywords: Hippocampus sparing, Alopecia, IMRT

Background

Cognitive impairment after WBRT is a significant problem with 50–90 % of patients showing measurable decline on testing and 10–15 % showing progressive clinical cognitive decline, with significant effect on quality of life [1–4]. While medical therapies (donapezil and memantine) have been used to prevent and treat cognitive decline associated with WBRT, they can be costly and may result in adverse effects or non-compliance [5, 6]. HS-WBRT has shown to be safe, feasible and promising in reducing cognitive decline [7–9].

HS-WBRT, usually performed with intensity modulation (IMRT), utilizes iterative planning to restrict dose to hippocampus while maintaining dose to the rest of the brain parenchyma as anatomically defined. The strict dose-volume parameters have been studied and prescribed in the recently completed and published RTOG trail, which showed significantly less decline in cognitive function with HS-WBRT [7].

Radiation induced alopecia is well-known and significant side effect of conventional WBRT [10, 11]. While the significance of radiation-induced alopecia has been
recognized, and attempts been made to mitigate or prevent it, it has been accepted as an unavoidable consequence. Dose response to alopecia [12] and other interventions to mitigate alopecia have been described. We report dose volume analysis to scalp, comparing conventional and HS-WBRT. This was in response to noticing hair preservation in all our patients treated with an 11-field HS-WBRT.

Materials and Methods

Patients with brain metastasis who fulfill the eligibility criteria for RTOG 0933 were included in this study. No patients had preexisting alopecia, including systemic chemotherapy induced alopecia, and had a full complement of scalp hair. The first 6 consecutive patients who received HS-WBRT who were noticed to have full preservation of scalp hair on follow up were analyzed. All patients had diagnostic brain MRI with contrast. A thermoplastic mask immobilization was used with CT simulation. CT-MRI fusion was used for target volume delineation. A simplified and reproducible in-house 11-field IMRT plan, with 9 coplanar (0° couch angle) of 6MV photons and 2 coronal (90° couch angle) beams of 10MV photons were used. This was preferred to the recommended beam arrangements in the RTOG trial, which involved multiple gantry and couch angles. The suggested field setup in the RTOG trial and the setup used in this study are compared in Fig. 1. All dosimetric guidelines and parameters used in the RTOG 0933 trial were used and met. The dose volume constraints to the hippocampus, the hippocampus avoidance zone, brain parenchyma and the organs at risk – including the lenses, optic nerves and optic chiasm, were met for all patients. A representative treatment plan is shown in Fig. 2.

5 mm hair follicle bearing scalp was auto contoured in all CT hair follicle bearing scalp was auto contoured in all CT simulation image data sets retrospectively (Fig. 3). Conventional opposed lateral fields with MLC (Multi Leaf Collimator) blocks were applied to all image sets as would be used to treat with conventional WBRT with 6MV photons. The dose volume parameters to the follicle-bearing scalp for both plans were calculated.

All patients were followed one month after and three monthly there after until progression or death, with clinical examination including mini mental state and brain MRI. As these patients were treated outside protocol, a complete neuro-cognitive assessment battery of tests was not performed.

Paired t-test to compare the means was utilized using STATA® software (Statacorp LP, College Station, Texas 77845, USA).
The retrospective review was IRB approved – hence the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki, and the study does not violate the policies and/or procedures established by the Journal.

Results
Clinical outcomes
At the time of their one-month and last follow up all patients had full scalp hair preservation (Fig. 4), by their own subjective reporting and on clinical examination. All patients experience fatigue, but no other neurological toxicity. One patient died of a stroke, presumed unrelated, one month after HS-WBRT. Two patients had recurrent brain metastasis. No patients failed in the Hippocampus avoidance zone or in the skull base. All six patients had clinically preserved cognitive function.

Dosimetric outcomes
The mean, maximum, V24 (volume of follicle bearing scalp receiving 24 Gy) and V30 (volume of follicle bearing scalp receiving 30 Gy) for each patient are shown in Table 1. Compared to HS-WBRT, conventional WBRT delivered significantly higher mean dose to follicle bearing scalp (16.33 cGy vs. 22.42 cGy, \( p < 0.0001 \)). The volume of radiated hair bearing scalp receiving 24 Gy – V_{24} (9 cc vs. 44 ml, \( p < 0.0000 \)) and V_{30} (0.096 ml vs. 9 ml, \( p = 0.0106 \)) were also significantly higher. Dose Volume Histograms (DVHs) illustrating differences in the volume of hair follicle bearing scalp-receiving threshold dose for alopecia (V_{24}) and prescribed dose (V_{30}) are shown in Fig. 5.

Discussion
Radiation to scalp with sufficient doses can lead to alopecia [12]. Conventional WBRT does not seek to limit dose to scalp and causes alopecia. Hippocampus sparing WBRT while attempting to rigidly enforce dose compliance to brain and normal structures including the hippocampus.
and the hippocampus avoidance zone, can spare hair follicle bearing scalp of significant radiation and prevents alopecia.

WBRT has long been the standard of care for brain metastasis. It significantly improves survival when indicated for prophylaxis [13, 14] and therapy [15]. Neurocognitive decline after WBRT is a recognized complication [16–18]. Attempts have been made to mitigate this with adjuvant medication modulating neurotransmission [5, 6]. Medication to prevent cognitive decline after WBRT can be costly, have problems with side effects and compliance and the benefits are modest. Randomized trials have also shown that addition of WBRT to local therapy (Stereotactic radiosurgery or resection) may not improve survival but significantly decreases the likelihood of distant brain failure [3, 4, 19, 20]. Hence there is a trend to omit WBRT altogether to avoid cognitive decline. However recurrent brain metastasis, which could have been prevented, can also be detrimental neurologically and may cause cognitive decline [21, 22]. With the realization of sensitive structures of the brain involved in neuro-cognitive processing in the Hippocampus area [9], and the likelihood of harboring metastasis or recurrence of metastasis in this zone being rare [8, 23], HS-WBRT has emerged as a viable treatment option to preserve the benefits of WBRT and yet decrease the probability of neuro-cognitive decline. Indeed a recently completed co-operative group trial confirmed the feasibility and the neuro-cognitive protective function of HS-WBRT [7]. This strategy avoids the additional cost, side effects and frequent non-compliance associated with the medications for preventing and treating neuro-cognitive decline. Encouraged by this our group initiated HS-WBRT for patients meeting the eligibility in this trial.

HS-WBRT has been shown to be feasible by multiple groups, with or without integrated boost using linear accelerator-based multi-field IMRT [24], Volumetric Modulated Arc Therapy (VMAT) [25–27] or Tomotherapy techniques [28]. Specific IMRT techniques have been
recommended and used in the RTOG 0933 trial [24].
However the 9-Field IMRT technique recommended in
this trial with multiple individual couch angles ranging
from 6°–354° and multiple individual gantry angles from
9°–319° were found, by us, to be unwieldy, cumbersome,
time consuming and fraught with potential collision and
setup errors. After experimenting with multiple simple
beam arrangements we found it feasible to reproducibly
achieve all DVH constraints as prescribed, with two fixed
standard couch position in 0° and 90° and fixed coplanar
gantry angles, thereby eliminating collision risk and sig-
nificantly simplifying and shortening of patients’ setup.

Tolerance dose to scalp has been reported for perman-
ent alopecia after definitive radiation therapy for brain tu-
mors [12, 29]. Hair loss, at least temporarily, occurs in
most patients receiving WBRT with conventional fraction-
ation [11]. This has been consistently shown to translate
to poor quality of life within their reduced life expectancy
in these patients [10, 14, 30, 31]. Attempts have been made
to use topical nitroxides [32, 33], prostaglandin E [34],
botulinum toxin [35] and vasoconstrictors [36] to decrease
the incidence and severity of alopecia after radiation ther-
apy. However the no clinical benefit was found. Scalp
dose-limiting WBRT techniques have been described pre-
viously. Roberge et al. measured surface scalp doses with
TLD and calculated doses at 5 mm thickness and reported
decrease in mean doses of 53 % and 38 % respectively
[37]. Mancini et al. similarly demonstrated decrease scalp
dose after VMAT-IMRT [38]. In a more detailed analysis
De Puysseleyn et al., using preliminary cadaveric data and
in a prospective study using VMAT IMRT for scalp
sparing, showed 37 % reduction to the median dose
to the hair follicle volume [39]. However, this unfortu-
nately did not translate into clinical benefit with poor
QOL and Alopecia scores. Differences in technique
(VMAT vs. Tomotherapy vs. Multi Field IMRT), energy,
beam arrangement, objectives (hippocampus sparing vs.
scalp sparing), contouring of hair bearing scalp, DVH

### Table 1 Hair follicle bearing scalp dose in cGy

| Patient | LATS Mean | HS-WBRT Mean | LATS Max | HS-WBRT Max | $V_{24}$ LATS | $V_{24}$ HS-WBRT | $V_{30}$ LATS | $V_{30}$ HS-WBRT |
|---------|-----------|---------------|----------|-------------|--------------|----------------|--------------|----------------|
| 1       | 2364.8    | 1189.7        | 3586.7   | 2997.8      | 51.94        | 0.26           | 23.71        | 0              |
| 2       | 2247.7    | 1715.6        | 3375     | 3795.5      | 45.59        | 11.5           | 6.84         | 0.21           |
| 3       | 2282.1    | 1623.9        | 3383.2   | 3107.8      | 46.2         | 6.47           | 6.77         | 0.01           |
| 4       | 2171.2    | 1827          | 3333.7   | 3280.6      | 40.16        | 16.69          | 3.94         | 0.21           |
| 5       | 2313.2    | 1646.7        | 3418     | 3352.1      | 50.59        | 10.56          | 11.62        | 0.08           |
| 6       | 2076      | 1797.4        | 3205.8   | 3238.7      | 30.33        | 13.38          | 1.17         | 0.07           |
| Mean    | 2242.5    | 1633.383      | 3383.733 | 3295.417    | 44.135       | 9.81           | 9.008333     | 0.096667       |

**Notes:**
- LATS: Opposed lateral fields
- HS-WBRT: Hippocampus sparing – whole brain radiation therapy
- $V_{24}$: Volume of hair bearing skin receiving 24 Gy in cc
- $V_{30}$: Volume of hair bearing skin receiving 30 Gy in cc

*Statistically significant

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**Fig. 5** Dose Volume Histogram showing scalp dose with conventional WBRT (dashed line) and HS-WBRT (solid line)
constraints and DVH parameters could account for the apparent differences in these outcomes.

Conclusion
While other IMRT set-ups have independently shown hippocampus sparing or scalp sparing, in our study we demonstrate dual benefit of hippocampus sparing and, unexpectedly, scalp sparing effects of an 11-field IMRT technique. This is likely to even more enhance the quality of life in suitable patients receiving WBRt for brain metastasis, and will be worthy of evaluating prospectively.

Abbreviations
HS-WBRT: hippocampus sparing WBRT; IMRT: intensity modulated radiation therapy; WBRt: whole brain radiation therapy.

Competing interests
None of the authors report any competing interests.

Authors’ contributions
AM designed the study, treated the patients, drafted and edited the manuscript. CS and SL contributed the dosimetric aspects of the study. EUEH, SS and EK assisted in drafting and editing the manuscript. All authors read and approved the final manuscript.

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