Automatic planning on hippocampal avoidance whole-brain radiotherapy

Shuo Wang, Ph.D., Dandan Zheng, Ph.D., Chi Zhang, M.D., Ph.D., Rongtao Ma, M.Sc., Nathan R. Bennion, M.D., Yu Lei, Ph.D., Xiaofeng Zhu, Ph.D.,1 Charles A. Enke, M.D., and Sumin Zhou, Ph.D.

Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE

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ABSTRACT

Mounting evidence suggests that radiation-induced damage to the hippocampus plays a role in neurocognitive decline for patients receiving whole-brain radiotherapy (WBRT). Hippocampal avoidance whole-brain radiotherapy (HA-WBRT) has been proposed to reduce the putative neurocognitive deficits by limiting the dose to the hippocampus. However, urgency of palliation for patients as well as the complexities of the treatment planning may be barriers to protocol enrollment to accumulate further clinical evidence. This warrants expedited quality planning of HA-WBRT. Pinnacle3 Automatic treatment planning was designed to increase planning efficiency while maintaining or improving plan quality and consistency. The aim of the present study is to evaluate the performance of the Pinnacle3 Auto-Planning on HA-WBRT treatment planning. Ten patients previously treated for brain metastases were selected. Hippocampal volumes were contoured on T1 magnetic resonance (MR) images, and planning target volumes (PTVs) were generated based on RTOG0933. The following 2 types of plans were generated by Pinnacle3 Auto-Planning: the one with 2 coplanar volumetric modulated arc therapy (VMAT) arcs and the other with 9-field noncoplanar intensity-modulated radiation therapy (IMRT). D2% and D98% of PTV were used to calculate homogeneity index (HI). HI and Paddick Conformity index (CI) of PTV as well as D100% and Dmax of the hippocampus were used to evaluate the plan quality. All the auto-plans met the dose coverage and constraint objectives based on RTOG0933. The auto-plans eliminated the necessity of generating pseudostructures by the planners, and it required little manual intervention which expedited the planning process. IMRT quality assurance (QA) results also suggest that all the auto-plans are practically acceptable on delivery. Pinnacle3 Auto-Planning generates acceptable plans by RTOG0933 criteria without time-consuming planning process. The expedited quality planning achieved by Auto-Planning (AP) may facilitate protocol enrollment of patients to further investigate the hippocampal-sparing effect and be used to ensure timely start of palliative treatment in future clinical practice.

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Introduction

Whole-brain radiation therapy (WBRT) is a well-established treatment for patients with brain metastases by radiologically controlling both visible tumors and nonvisible micrometastases.1 Despite being the mainstay of the treatment, WBRT has been reported to cause long-term, progressive, and irreversible neurologic sequelae, including leukoencephalopathy, cognitive deterioration, cerebellar dysfunction, and dementia.2–4 Recent evidence also suggests that debilitating neurocognitive function can occur months after therapy.5 Specifically, it has been documented that patients who received WBRT can present with progressively severe deficits in learning, memory, and spatial processing.6,7 Recently, these radiation-induced neurocognitive function deficits have been associated with radiation-induced injury to the proliferating neuronal progenitor cells in the subgranular zone of the hippocampi.8–10 Furthermore, data for patients receiving radiation therapy for brain malignancies and head-and-neck cancers11–14 have also demonstrated the association between cognitive impairment and radiation received in the hippocampal area. Though the
underlying mechanisms are still not fully understood, preclinical studies reveal that the highly radiosensitive nature of the neural stem cell compartment (stem cell niche) putatively represents one possible mechanism causing impaired neurogenesis in the hippocampus. Radiation-induced injury, particularly inflammation, has been suggested to cause structural alterations to the hippocampal microenvironment, thereby regulating the fate of the neural progenitor cells. All of the preclinical and clinical evidence led the proposed hippocampal-sparing WBR by RTOG0933, which putatively circumscribe the radiation-induced inflammation by reducing the dose to the hippocampi. Nevertheless, hippocampal-sparing could pose the risk of diminishing the clinical benefit of WBR if metastases lie within the spared region. Although recent clinical data showed that the estimated perihippocampal metastasis risk is likely overestimated, we need larger sample sizes to better understand the risks and benefits of hippocampal avoidance WBRT (HA-WBR). Hippocampal-sparing techniques pose challenges with respect to the treatment planning owing to the anatomical shape and location of the hippocampus. The planning time can be considerably longer than that of conventional WBRT planning. Complicating this task, patients with brain metastases often necessitate timely palliation. Thus, the urgency of palliation as well as the complexities of the treatment planning may be barriers to protocol enrollment to accumulate further clinical evidence. Recent dosimetric studies have documented treatment planning experience on HA-WBR. Gondi et al.34 have reported the planning experience of HA-WBR using helical tomotherapy and noncoplanar static intensity-modulated radiation therapy (IMRT) beams with a linear accelerator. Lagerwaard et al.35 have also developed planning techniques using RapidArc. Siglin et al.36 also demonstrated that dosimetric improvements could be achieved by optimized patient positioning. Nonetheless, patient-specific anatomy and planners’ experience could result in inconsistent plan quality and time-consuming planning process.

Auto-Planning (AP) is a volume-driven automatic planning platform, which is recently released in Pinnacle® Treatment planning system (TPS) (Philips Medical Systems, Fitchburg, WI). It is designed to improve the planning efficiency and maintain or improve the plan quality. It uses progressive optimization to create planning structures based on desired target coverage and organs at risk (OAR) sparing as well as anatomical relationships among the planning target volumes (PTVs) and OARs, and iteratively prioritize and adjust the planning objectives during optimization. Pinnacle® Auto-Planning has been documented to generate acceptable plans by generating acceptable plans without delaying the patient treatment. The aim of the present study is to evaluate the performance of the Auto-Planning on HA-WBRT treatment planning.

Methods and Materials

Patient selection

Ten patients were selected for the present retrospective study with approval from institutional review board (IRB# 341-16-EP).

Simulation and structure contouring

Patients were simulated using a Sensation Open computed tomography (CT) system (Siemens Medical Solutions USA, Malvern, PA). Each patient also underwent high-resolution 3D contrast-enhanced T1-weighted magnetic resonance imaging. The hippocampi were contoured manually on T1W-MRI, and other anatomical structures were delineated on the fused CT and magnetic resonance images in the BrainLab iPlan TPS, version 4.5 (BRAINLAB AG, Feldkirchen, Germany). CT images with the associated structure sets were transferred to Pinnacle® TPS (version 9.10, Philips Medical Systems, Fitchburg, WI) using the DICOM-RT protocol. A 5-mm 3D expansion was applied to the hippocampi to generate hippocampal avoidance regions. The whole-brain PTV (WB_PTV) was generated as the whole-brain parenchyma to C1 or C2 excluding hippocampal avoidance regions based on RTOG0933.

Table 1

<table>
<thead>
<tr>
<th>Beam</th>
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<td>9</td>
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</table>

Quality assurance of the auto-plans

IMRT quality assurance (QA) measurements for all the cases were performed and gamma analysis was used to evaluate the agreement between the measured dose distribution and calculated dose distribution. The treatment plans were delivered on a TrueBeam STx linear accelerator (Varian Medical Systems, Palo Alto, CA). The Auto-VMAT plans were measured by ArcCHECK diode array (Sun Nuclear Cooperation, Melbourne, FL).37-39 and the Auto-SIMRT plans were measured by MatrixXX ion chamber array (IBA Dosimetry, Bartlett, TN).37 Comparisons were performed by the use of the gamma analysis with different dose and distance criteria,12,31 respectively. 

<table>
<thead>
<tr>
<th>Criterion</th>
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<td>D2%</td>
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<td>Dmean</td>
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<tr>
<td>Dmax</td>
<td>Dmax_ref - Dmax_measured</td>
</tr>
<tr>
<td>Homogeneity index (HI)</td>
<td>Defined as D98% minus D2% divided by prescription dose (HI = D98% - D2%)</td>
</tr>
<tr>
<td>Paddick conformity index (CI)</td>
<td>Defined as D98% minus D2% divided by prescription dose (CI = D98% - D2%)</td>
</tr>
</tbody>
</table>

(A) 9-Field IMRT beam arrangement

(B) Coplanar arc beam arrangement

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Results

**Target coverage, homogeneity, and conformity of WB_PTV**

Auto-VMAT plans had a $D_{2\%}$ of 3512 ± 28 cGy, $D_{98\%}$ of 2662 ± 62 cGy, and $V_{100}$ of 91.49 ± 0.56%. Auto-9IMRT plans had a $D_{2\%}$ of 3510.5 ± 27.3 cGy, $D_{98\%}$ of 2719.9 ± 82.5 cGy, and $V_{100}$ of 92.94 ± 0.81%. All of the parameters complied with the PTV coverage criteria from RTOG0933. Figure 1 presents cumulative normalized dose-volume histograms for all the auto-plans for HA-WBRT (N = 10). Figure 2 shows the representative spatial isodose distribution at the level of hippocampi. Table 2 lists the $D_{2\%}$, $D_{98\%}$, $V_{100}$, homogeneity index, and conformity index of WB_PTV. Furthermore, $V_{90}$ and $V_{95}$ for both the plans using different beam setups (Table 2) are comparable with the previous study.18

**Dose to hippocampus, lenses, and optic nerves**

Table 3 lists $D_{100\%}$, maximum doses to individual hippocampus as well as the maximum doses to the lenses and optic nerves. Generally, Auto-9IMRT plans have better OAR sparing and better conformity than Auto-VMAT plans at the expense of inferior homogeneity of the dose distribution.

![Fig. 1.](A) Normalized dose-volume histograms for auto-plans (9F-IMRT). (B) Normalized dose-volume histograms for auto-plans (2 coplanar arcs). Here, purple line represents whole-brain PTV, green line represents right hippocampus, and red line represents left hippocampus. (Color version of figure is available online.)

![Fig. 2.](A1-A3) Isodose distribution. Spatial isodose distribution for a sample patient whose plan has the $V_{30}$ close to mean value at the level of the hippocampi for HA-WBRT using 9-field IMRT (A1-A3) and 2 coplanar arc VMAT (B1-B3). Black contours represent the hippocampus. Dark red isodose represents 9 Gy; purple line represents 16 Gy; dark green line represents 25 Gy; yellow line represents 30 Gy (Rx dose); and red lines represents 37.5 Gy if any. (Color version of figure is available online.)
the phase III setting to further corroborate the promising results treated with HA-WBRT, this technique is likely to be expanded in memory preservation observed in patients with brain metastases. Therefore, conformal avoidance of the hippocampi is required to achieve neuroprotective benefits while avoiding risk of disease progression. Second, treatment plans with consistent quality produced in a timely manner are also required, as rapid palliation is necessary to control the neurologic symptoms and assess the neuroprotective effects of hippocampal avoidance on longer-term sequelae of WBRT in a larger sample size. Clinical implementation of HA-WBRT, however, has posed important challenges. First, accurate delineation of the hippocampi is required to achieve neuroprotective benefits while avoiding risk of disease progression. Second, treatment plans with consistent quality produced in a timely manner are also required, as rapid palliation is necessary to control the neurologic symptoms for patients with brain metastases. Third, effort is warranted to reduce treatment times and the possibility of operating errors. Knowing the added cost and complexities, continued research and assess the neuroprotective effects of hippocampal avoidance on longer-term sequelae of WBRT in a larger sample size. Clinical implementation of HA-WBRT, however, has posed important challenges. First, accurate delineation of the hippocampi is required to achieve neuroprotective benefits while avoiding risk of disease progression. Second, treatment plans with consistent quality produced in a timely manner are also required, as rapid palliation is necessary to control the neurologic symptoms for patients with brain metastases. Third, effort is warranted to reduce treatment times and the possibility of operating errors. Knowing the added cost and complexities, continued research and assess the neuroprotective effects of hippocampal avoidance on longer-term sequelae of WBRT in a larger sample size.

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effort has been placed on this area. 16–18 We herein report our initial experience of using Pinnacle3 Auto-Planning on HA-WBRT planning and evaluate the potential of it as an effective way for HA-WBRT treatment planning with consistent plan quality.

Among the 10 studied cases, Auto-Planning resulted in treatment plans that complied with the dosimetric criteria by RTOG0933. Specifically, on average, D2% of WB_PTV was 3333.7 cGy (VMAT) and 3510.5 cGy (IMRT) with relatively small standard deviations (± 29.6 cGy and ± 27.3 cGy), which were substantially lower than the protocol requirement of 3750 cGy. Similarly, D98% of WB_PTV was measured at 2775.5 cGy (VMAT) and 2719.9 cGy (IMRT), which also satisfied the protocol criteria (2500 cGy). Furthermore, Auto-9IMRT plans attained comparable plan quality (V95 and V90) as published previously.18 Both the Auto-VMAT plans and Auto-9IMRT plans met the critical structure avoidance WBRT.

As shown in Figure 1, Auto-9IMRT plans resulted in plans with more consistent quality. Also, the optimization and calculation time to generate Auto-IMRT plans is significantly shorter than Auto-VMAT plans. On the contrary, Auto-VMAT plans can reduce treatment time and possible operating errors during the treatment, as two coplanar arcs are used.

Apart from dosimetric results, it is worth mentioning that 85% of cases were generated by Auto-Planning with a generic Auto-Plan constraint plans that complied with the dosimetric criteria by RTOG0933 (Table 2). Although further improvement might be necessary for the VMAT plans, the plans were still acceptable. As shown in Figure 1, Auto-9IMRT plans resulted in plans with more consistent quality. Also, the optimization and calculation time to generate Auto-IMRT plans is significantly shorter than Auto-VMAT plans. On the contrary, Auto-VMAT plans can reduce treatment time and possible operating errors during the treatment, as two coplanar arcs are used.

In summary, our initial experience has shown that Pinnacle3 Auto-Planning can represent an effective way to improve the HA-WBRT planning process with consistent plan quality. Also, successfully generating acceptable plans using both static IMRT and coplanar VMAT indicated that the treatment could be less dependent on the availability of delivering techniques. The QA results also revealed that all the auto-plans were practically acceptable for patient care. Therefore, Auto-Planning could contribute to provide effective solutions to some of the aforementioned technical hurdles. Especially, as a bread-and-butter case for palliative radiotherapy, whole-brain radiotherapy conventionally involves expeditious simulation-to-treatment timeline and a relatively light demand on resources in terms of dosimetry time and treatment time. Should HA-WBRT become a routine standard of care, the Auto-VMAT plans with coplanar arcs as demonstrated in our study could be an ideal solution that imposes minimal additional burden for treatment planning and delivery time beyond the current WBRT. However, owing to our limited sample size, further studies are necessary before broad implementation of Pinnacle3 Auto-Planning for HA-WBRT.

Moreover, we did not systematically evaluate the design and current limitations or provide any insights on potential improvement of this automated planning platform, partially owing to inadequate access and resources to experiment on this commercially available module as a prototype.

In summary, our initial experience has shown that Pinnacle3 Auto-Planning could represent an effective way to generate treatment plans with consistent plan quality for hippocampal avoidance WBRT.

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References


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