

5-25-2024

Radiotherapy Plan Quality Assurance in NRG Oncology Trials for Brain and Head/Neck Cancers: An AI-Enhanced Knowledge-Based Approach

Du Wang

Huaizhi Geng

Vinai Gondi

Nancy Lee

Christina Tsien

See next page for additional authors

Follow this and additional works at: <https://jdc.jefferson.edu/radoncfp>



Part of the [Oncology Commons](#), and the [Radiation Medicine Commons](#)

[Let us know how access to this document benefits you](#)





This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Radiation Oncology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

Du Wang, Huaizhi Geng, Vinai Gondi, Nancy Lee, Christina Tsien, Ping Xia, Thomas Chenevert, Jeff Michalski, Mark Gilbert, Quynh-Thu Le, Antonio Omuro, Kuo Men, Kenneth Aldape, Yue Cao, Ashok Srinivasan, Igor Barani, Sean Sachdev, Jiayi Huang, Serah Choi, Wenyin Shi, James Battiste, Zabi Wardak, Michael Chan, Minesh Mehta, and Ying Xiao

Article

Radiotherapy Plan Quality Assurance in NRG Oncology Trials for Brain and Head/Neck Cancers: An AI-Enhanced Knowledge-Based Approach

Du Wang ^{1,*}, Huaizhi Geng ¹, Vinai Gondi ², Nancy Y. Lee ³, Christina I. Tsien ⁴, Ping Xia ⁵, Thomas L. Chenevert ⁶, Jeff M. Michalski ⁷, Mark R. Gilbert ⁸, Quynh-Thu Le ⁹, Antonio M. Omuro ⁹, Kuo Men ¹, Kenneth D. Aldape ⁸, Yue Cao ⁶, Ashok Srinivasan ⁶, Igor J. Barani ¹⁰, Sean Sachdev ², Jiayi Huang ⁷, Serah Choi ¹¹, Wenyin Shi ¹², James D. Battiste ¹³, Zabi Wardak ¹⁴, Michael D. Chan ¹⁵, Minesh P. Mehta ¹⁶ and Ying Xiao ¹

¹ Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA 19104, USA; ying.xiao@pennmedicine.upenn.edu (Y.X.)

² Northwestern Medicine Cancer Center Warrenville, Warrenville, IL 60555, USA

³ Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

⁴ McGill University Health Centre, Montreal, QC H4A 3J1, Canada

⁵ Cleveland Clinic Foundation, Cleveland, OH 44195, USA

⁶ Department of Radiology, University of Michigan, Ann Arbor, MI 48109, USA; tlchenev@umich.edu (T.L.C.)

⁷ Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA

⁸ National Cancer Institute, Bethesda, MD 20892, USA

⁹ Stanford Cancer Institute, Stanford, CA 94305, USA; qle@stanford.edu (Q.-T.L.)

¹⁰ Saint Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

¹¹ UPMC-Shadyside Hospital, Case Western Reserve University, Pittsburgh, PA 15232, USA

¹² Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA

¹³ Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA

¹⁴ UT Southwestern, Simmons Cancer Center, Dallas, TX 75235, USA

¹⁵ Baptist Comprehensive Cancer Center, Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA

¹⁶ Miami Cancer Institute, Miami, FL 33176, USA

* Correspondence: du.wang@pennmedicine.upenn.edu; Tel.: +1-267-353-1497



Citation: Wang, D.; Geng, H.; Gondi, V.; Lee, N.Y.; Tsien, C.I.; Xia, P.; Chenevert, T.L.; Michalski, J.M.; Gilbert, M.R.; Le, Q.-T.; et al. Radiotherapy Plan Quality Assurance in NRG Oncology Trials for Brain and Head/Neck Cancers: An AI-Enhanced Knowledge-Based Approach. *Cancers* **2024**, *16*, 2007. <https://doi.org/10.3390/cancers16112007>

Academic Editor: Andreas Stadlbauer

Received: 3 April 2024

Revised: 15 May 2024

Accepted: 19 May 2024

Published: 25 May 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Simple Summary: Radiation therapy (RT) plans deviating from the standard could likely compromise the efficacy of a pre-specified intervention for any clinical trial due either to insufficient coverage of the target area and/or excessive radiation doses to healthy tissues. Knowledge-based machine learning tools utilize high-quality data and generate patient-specific optimization objectives that produce RT plans that comply better with treatment protocol specifications. In this study, we investigated the use of a knowledge-based planning (KBP) model to evaluate the quality of RT plans in two clinical trials, one for glioblastoma and the other for head and neck cancer. The outcomes of this research indicate that this tool can assist RT quality assessments in multi-center clinical trials.

Abstract: The quality of radiation therapy (RT) treatment plans directly affects the outcomes of clinical trials. KBP solutions have been utilized in RT plan quality assurance (QA). In this study, we evaluated the quality of RT plans for brain and head/neck cancers enrolled in multi-institutional clinical trials utilizing a KBP approach. The evaluation was conducted on 203 glioblastoma (GBM) patients enrolled in NRG-BN001 and 70 nasopharyngeal carcinoma (NPC) patients enrolled in NRG-HN001. For each trial, fifty high-quality photon plans were utilized to build a KBP photon model. A KBP proton model was generated using intensity-modulated proton therapy (IMPT) plans generated on 50 patients originally treated with photon RT. These models were then applied to generate KBP plans for the remaining patients, which were compared against the submitted plans for quality evaluation, including in terms of protocol compliance, target coverage, and organ-at-risk (OAR) doses. RT plans generated by the KBP models were demonstrated to have superior quality compared to the submitted plans. KBP IMPT plans can decrease the variation of proton plan quality and could possibly be used as a tool for developing improved plans in the future. Additionally, the KBP tool proved to be an effective instrument for RT plan QA in multi-center clinical trials.

Keywords: radiotherapy; knowledge-based planning; brain and head/neck cancers; clinical trial quality assurance

1. Introduction

Glioblastoma is the most aggressive primary malignant brain tumor found in humans, with 5-year overall survival less than 7% after surgery and conventional chemoradiotherapy [1,2]. The conventional therapeutic regimen for GBM comprises resection to the greatest extent safely feasible, followed by concurrent and adjuvant temozolomide (TMZ) chemotherapy and RT [3–5]. Despite enhancements in patient survival with this combinatorial approach, local disease control remains a challenge and a major cause of therapeutic failure [6]. In an endeavor to improve outcomes, NRG Oncology initiated the phase II randomized trial NRG-BN001 to assess the impact of escalated RT doses in conjunction with TMZ for GBM patients. This trial also aims to compare the benefits of proton beam therapy versus photon IMRT, potentially enabling higher RT doses without escalating toxicity and specifically diminishing the risk of lymphopenia, which is supported by level 1 evidence. Indirect data suggest reduced survival with more severe lymphopenia.

Nasopharyngeal carcinoma (NPC) poses significant challenges for RT planning due to the complexity of planning target volumes (PTVs), the necessity for simultaneous integrated boost techniques, and the imperative of sparing multiple OARs [7,8]. NRG-HN001, a phase II/III multi-institutional clinical trial, targets patients diagnosed with NPC to investigate and optimize therapeutic strategies. In addition, both NRG-BN001 and NRG-HN001 represent pivotal investigations into the application of proton therapy within phase III clinical trials. The results of these trials are anticipated to provide evidence regarding whether proton therapy can positively influence patient outcomes, specifically in terms of augmenting efficacy and/or decreasing toxicities.

The correlation between adherence to established guidelines in RT treatment planning and clinical outcomes is well-documented; deviations from such protocols are linked with diminished survival rates, increased probability of disease progression, and a greater risk of RT-induced complications. Consequently, rigorous QA of RT plans is a pivotal QA component for clinical trials that incorporate RT [9–11].

The Imaging Radiation Oncology Core (IROC) of the National Clinical Trials Network has conducted QA reviews of all treatment plans of patients enrolled in NRG Oncology clinical trials. Although this process can easily identify plans that deviate from protocol-defined criteria, it does not capture the intricacies and challenges inherent in individual patient plans. Moreover, the current IROC QA process does not offer insights or possibilities for enhancing the quality of the treatment plans.

The rapid development of Artificial Intelligence (AI) in recent years offers a promising solution to these challenges. Knowledge-based planning (KBP) is a specialized application of AI designed to improve radiation therapy planning by using historical data to build predictive models. These models, trained on high-quality, protocol-compliant plans, learn the optimal dosimetric parameters based on patient geometry, enabling the creation of customized radiation therapy (RT) plans [12,13]. KBP significantly reduces the variability that often arises in RT planning from differences in planner experience and institutional practices [14–17]. By providing a data-driven benchmark for plan quality, KBP promotes consistency and efficiency in plan evaluation across multiple treatment centers, which is particularly valuable in multi-center clinical trials.

Although several recent publications have shown the feasibility of KBP-assisted intensity-modulated radiation therapy (IMRT) treatment planning in clinical settings [17–22], implementing knowledge-based proton planning in clinical trial evaluation is in its infancy [23]. Prior research has illuminated the application of the KBP model in evaluating the quality of photon plans submitted to NRG-HN001. Building on this foundation, our current study aims to extend the evaluation framework to include both photon and proton treatment plans

submitted to the NRG-BN001 trial as well as to assess the quality of NRG-HN001 IMPT plans utilizing a knowledge-based approach. This comprehensive assessment seeks to leverage the insights gleaned from KBP models to ensure and enhance the quality of treatment plans across different modalities and clinical scenarios.

2. Materials and Methods

2.1. Patient Cohort

This research incorporated a study population of 203 patients diagnosed with glioblastoma (GBM) who were part of the NRG-BN001 clinical trial and 70 patients with nasopharyngeal carcinoma (NPC) who participated in the NRG-HN001 study. In the context of the NRG-BN001 trial, 139 patients received photon therapy, and 64 patients received proton therapy, with both groups undergoing dose-intensified radiotherapy with a simultaneous Integrated Boost. This latter group was further divided into 36 cases treated with IMPT and 28 cases undergoing passive scattered (PS) proton therapy. All participants in this trial were prescribed 50 Gy (relative biological effectiveness [RBE] for protons) in 30 fractions to the FLAIR or T2 abnormality, with a simultaneous integrated boost to 75 Gy ([RBE] for protons) to the postoperative cavity and residual enhancing disease. Regarding the NRG-HN001 trial, there were 50 patients treated with IMRT and 20 patients treated with proton therapy. The prescribed dose was either 69.96 Gy in 33 fractions or 70 Gy in 35 fractions. Both trials set forth specific dosimetric compliance standards. These standards, relevant to both targets and OARs, are elaborated in Supplementary Table S1 and Supplementary Table S2, respectively. Any structures not complying with the protocol's accepted variation thresholds are categorized as unacceptable deviations.

2.2. Knowledge-Based Planning and Model Configuration

2.2.1. Photon Model

Fifty per-protocol IMRT plans from the NRG-BN001 photon group were chosen to develop the photon RapidPlan[®] RT (Varian Medical System, Palo Alto, CA, USA) model. The initial parameters of the model were established in accordance with the priorities provided in the protocol. Structures assigned a higher priority level were given a greater priority value. These same plans also served as an internal validation cohort, aiding in the refinement of model parameters. The final KBP photon model's defined objective list is detailed in Supplementary Table S3. For the re-optimization of photon plans, the Photon Optimizer (PO) for IMRT (version 16.0.2), the Dose-Volume Histogram (DVH) Estimation Algorithm (version 16.0.2) for DVH estimation, and the Anisotropic Analytical Algorithm (AAA, version 16.0.2) for volume and portal dose computation were selected as the calculation models.

2.2.2. Proton Models

For each trial, fifty patients enrolled in photon cohorts were manually re-planned with the IMPT technique using golden beam data of the ProBeam proton therapy system. The volume dose was calculated based on the Proton Convolution Superposition algorithm (PCS, v. 16.0.2) with a 5 mm spot size and 2.5 mm resolution. The fluence-based Nonlinear Universal Proton Optimizer (NUPO, v. 16.0.2) and the multifield simultaneous spot optimization method were applied to optimize dose distribution.

The 50 manually generated IMPT plans were evaluated based on the dosimetric compliance criteria specified in each protocol and were subsequently utilized to train the preliminary models. To enhance the performance of these models, a closed-loop iteration was implemented by re-optimizing the library IMPT plans using the initial RP model and updating the model with the re-optimized cases. For NRG-BN001, the KBP IMPT models also include three control regions aimed at optimizing the dose distribution. These additional regions comprised the Planning Risk Volume (PRV), defined as PTV_5000 minus (PTV_7500 plus a 5 mm margin); PTV_5000 opt, delineated as PTV_5000 excluding PTV_7500; and a 'ring' region, specified as a 1 cm margin encircling PTV_5000. Supplemen-

tary Tables S3 and S4 list the optimization objectives and priorities specified in the final KBP proton model for NRG-BN001 and NRG-HN001, respectively.

2.3. Plan Evaluation

The plan quality of the submitted photon and proton plans was assessed through comparison with the KBP photon and proton plans. The evaluation was conducted based on protocol compliance, target dose conformality index (CI) and homogeneity index (HI), and the dosimetric endpoints, including PTVs and critical structures [24,25]. IROC has developed a QA workflow to evaluate RT plans. This systematic approach assesses adherence to the protocol-defined dose constraints and categorizes RT plans into three distinct scores: per-protocol: score 1, variation acceptable: score 2, and deviation unacceptable: score 3.

The conformality index was calculated based on the Paddick index [26], defined as:

$$CI = \frac{TV_{PIV}^2}{PIV \times TV} \quad (1)$$

where TV_{PIV} is the target volume encompassed by the prescription isodose, PIV is the prescription isodose volume, and TV is the target volume. The homogeneity index was defined as the ratio of the maximum point dose D_{max} and the prescribed dose D_{Rx} [27]:

$$HI = \frac{D_{max}}{D_{Rx}} \quad (2)$$

To evaluate the differences in quality between the plans submitted initially and those derived from KBP, mean dosimetric parameters were assessed. Furthermore, a paired T-test was employed to conduct a statistical comparison.

3. Results

3.1. NRG-BN001 Photon Plan Quality Review

Table 1 lists the results of the 139 photon plans submitted to NRG-BN001 using the IROC QA procedure before and after KBP model optimization. The KBP plans show substantially better quality; the number of cases that failed to meet the per-protocol and variation acceptable criteria dropped by 39% and 60.1%, respectively.

Table 1. Comparison of IROC QA scores between the submitted NRG-BN001 photon plans and the KBP plans.

Structures	Dosimetric Parameter	Photon Submitted			Photon KBP		
		Score 1	Score 2	Score 3	Score 1	Score 2	Score 3
PTV_5000	D95%[Gy]	110	27	2	130	9	0
PTV_7500	D95%[Gy]	105	26	8	111	19	9
PTV_7500	D10%[Gy]	101	35	3	138	1	0
PTV_7500	D0.03cc[Gy]	84	47	8	126	13	0
SpinalCord	D0.03cc[Gy]	139	0	0	139	0	0
BrainStemCore	D0.03cc[Gy]	125	13	1	126	13	0
BrainStemSurf	D0.03cc[Gy]	121	18	0	124	15	0
OpticChiasm_PRV	D0.03cc[Gy]	129	10	0	130	9	0
OpticNerve_L_PRV	D0.03cc[Gy]	135	3	1	134	5	0
OpticNerve_R_PRV	D0.03cc[Gy]	133	5	1	132	6	1
Retina_L	D0.03cc[Gy]	138	1	0	139	0	0
Retina_R	D0.03cc[Gy]	139	0	0	137	2	0
Brain	D5% [Gy]	136	2	1	139	0	0
Lens_L	D0.03cc[Gy]	126	11	2	118	20	1
Lens_R	D0.03cc[Gy]	126	12	1	123	16	0

Score 1: per-protocol; Score 2: variation acceptable; Score 3: deviation unacceptable.

Table 2 presents a detailed dosimetric comparison between the initially submitted intensity-modulated radiation therapy (IMRT) plans and the KBP plans. On average, both groups of plans demonstrate satisfactory target coverage, adhering to the specified protocol constraints for all anatomical structures. There is a notable equivalence in target dose coverage (PTV_7500 D95%[Gy]: $\Delta = 0.2 \pm 1.9$ Gy), conformality index ($\Delta = 0.0 \pm 0.20$), and the homogeneity index ($\Delta = -0.02 \pm 0.03$) between the submitted and KBP plans. The application of KBP is particularly advantageous for organs of higher priority, as it facilitates a reduction in dosage. This improvement is evident in the spinal cord ($\Delta = -0.9 \pm 3.0$), brain stem_core/surf ($\Delta = -1.7 \pm 6.2$ and -2.2 ± 5.9), optic chiasm_PRV ($\Delta = -3.6 \pm 6.8$), and optic nerve_PRV ($\Delta = -2.6 \pm 5.8$). Figure 1 further illustrates this outcome, showcasing a dose wash comparison for an exemplary case from the photon cohort between the submitted and KBP plans.

Table 2. Dosimetric comparison of submitted and KBP photon plans for NRG-BN001.

Structures	Dosimetric Parameter	Photon Submitted	Photon KBP	<i>p</i> Value
PTV_5000	D95%[Gy]	50.9 ± 1.5	51.7 ± 1.2	<0.001 *
PTV_7500	D95%[Gy]	74.2 ± 2.9	74.0 ± 2.8	0.001 *
PTV_7500	D10%[Gy]	78.1 ± 1.6	76.7 ± 0.8	<0.001 *
PTV_7500	D0.03cc[Gy]	79.8 ± 1.9	78.5 ± 1.3	<0.001 *
Spinal Cord	D0.03cc[Gy]	6.6 ± 5.9	5.6 ± 5.1	<0.001 *
BrainStem_Core	D0.03cc[Gy]	46.6 ± 11.6	44.6 ± 14.0	0.019 *
BrainStem_Surf	D0.03cc[Gy]	46.1 ± 12.7	43.6 ± 14.7	<0.001 *
OpticChiasm_PRV	D0.03cc[Gy]	39.7 ± 16.3	35.9 ± 16.9	<0.001 *
OpticNerve_PRV	D0.03cc[Gy]	33.7 ± 20.1	31.1 ± 20.2	<0.001 *
Retina	D0.03cc[Gy]	16.4 ± 12.3	17.5 ± 12.1	0.054
Brain	D5% [Gy]	72.1 ± 7.0	72.42 ± 6.2	0.803
Lens	D0.03cc[Gy]	4.6 ± 2.7	5.3 ± 2.6	<0.001 *
HI _{PTV_7500}		1.06 ± 0.02	1.04 ± 0.02	<0.001 *
CI _{PTV_7500}		1.00 ± 0.18	1.00 ± 0.10	0.39

The paired *t*-test was employed; asterisks (*) indicate a statistically significant difference between the submitted and KBP plan.

3.2. NRG-BN001 Proton Plan Quality Review

Table 3 presents the IROC QA review results for the 64 proton plans submitted to NRG-BN001 and the KBP IMPT plans. The KBP plans show substantially better quality; the number of cases that failed to meet the per-protocol and variation acceptable criteria was reduced by 77.6% and 66.7%, respectively.

Table 4 methodically outlines the average variations in pivotal dosimetric parameters between the originally submitted proton plans and the KBP IMPT plans. Notably, the maximum dose imparted to the brain stem_core, brain stem_surf, optic chiasm_PRV, optic nerve_PRV, and retina demonstrated a significant reduction ($p < 0.05$) in the KBP IMPT plans. The reductions were quantified as 10.3 ± 6.1 Gy, 12.8 ± 8.2 Gy, 10.6 ± 10.2 Gy, 4.3 ± 5.3 Gy, and 4.2 ± 6.9 Gy for the IMPT group and 9.7 ± 9.6 Gy, 10.3 ± 8.6 Gy, 12.8 ± 13.2 Gy, 5.4 ± 8.0 Gy, and 4.1 ± 8.2 Gy for the PS group. Figure 2 provides a visual representation of the dose distribution for a typical case within the proton cohort. In comparison to the clinically submitted plan, the KBP IMPT plan exhibits significant enhancement in both target coverage and OAR sparing. However, it is noteworthy that the KBP plan is associated with an elevated maximum dose to the PTV and an increased volume of brain tissue subjected to radiation exposure.

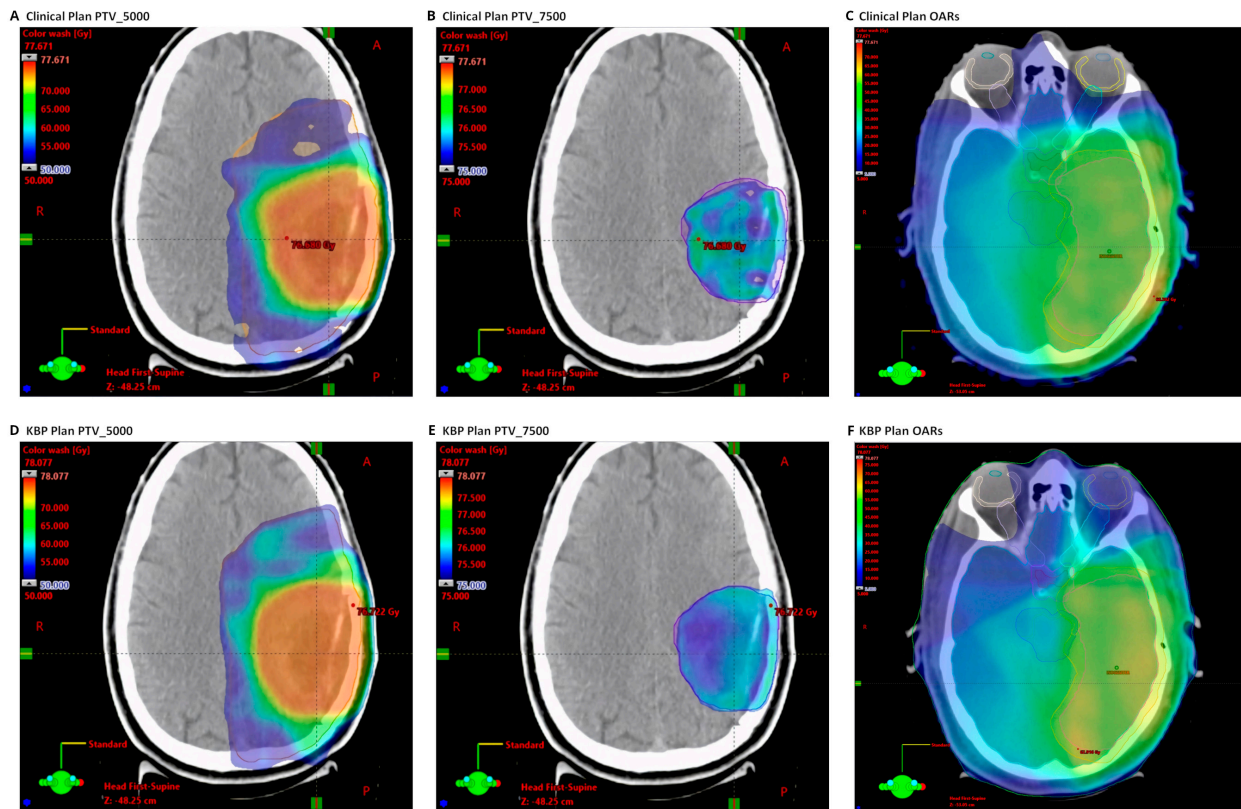


Figure 1. Dose distribution of an example case in the photon cohort. The clinical plan was the originally submitted plan and the KBP plan was generated using the IMRT RapidPlan model. (A–C) Dose distribution of the clinical plan. (D–F) Dose distribution of the KBP plan. The KBP plan demonstrates enhanced sparing of OARs with higher priority, including the brainstem, optic chiasm, and optic nerve.

Table 3. Comparison of IROC QA scores between the submitted NRG-BN001 proton plans and the KBP plans.

Structures	Dosimetric Parameter	Proton Submitted			Proton KBP		
		Score 1	Score 2	Score 3	Score 1	Score 2	Score 3
PTV_5000	D95%[Gy]	49	14	1	63	1	0
PTV_7500	D95%[Gy]	37	22	5	61	1	2
PTV_7500	D10%[Gy]	60	4	0	64	0	0
PTV_7500	D0.03cc[Gy]	63	1	0	57	7	0
SpinalCord	D0.03cc[Gy]	64	0	0	64	0	0
BrainStemCore	D0.03cc[Gy]	61	3	0	64	0	0
BrainStemSurf	D0.03cc[Gy]	58	6	0	63	1	0
OpticChiasm_PRV	D0.03cc[Gy]	62	2	0	63	1	0
OpticNerve_L_PRV	D0.03cc[Gy]	61	3	0	64	0	0
OpticNerve_R_PRV	D0.03cc[Gy]	62	1	1	62	1	1
Retina_L	D0.03cc[Gy]	64	0	0	64	0	0
Retina_R	D0.03cc[Gy]	63	0	1	64	0	0
Brain	D5%[Gy]	64	0	0	64	0	0
Lens_L	D0.03cc[Gy]	63	0	1	64	0	0
Lens_R	D0.03cc[Gy]	62	2	0	63	1	0

Score 1: per-protocol; Score 2: variation acceptable; Score 3: deviation unacceptable.

Table 4. Comparison of dosimetric parameters in submitted and KBP proton plans of BN001 clinical trial.

Structures	Dosimetric Parameter	IMPT			PS		
		Clinical	KBP	<i>p</i> Value	Clinical	KBP	<i>p</i> Value
PTV_5000	D95%[Gy]	50.9 ± 1.7	50.8 ± 0.4	0.772	50.3 ± 1.5	50.9 ± 0.35	0.037 *
PTV_7500	D95%[Gy]	73.3 ± 3.5	75.0 ± 1.4	<0.001 *	74.2 ± 1.5	75.2 ± 0.5	0.002 *
PTV_7500	D10%[Gy]	77.4 ± 0.8	77.5 ± 0.4	0.22	77.1 ± 1.5	77.5 ± 0.4	0.164
PTV_7500	D0.03cc[Gy]	78.4 ± 1.0	79.5 ± 0.8	<0.001 *	78.4 ± 1.8	79.3 ± 0.6	0.015*
Spinal Cord	D0.03cc[Gy]	0.1 ± 0.1	0.0 ± 0.0	0.005 *	0.1 ± 0.3	0.0 ± 0.0	0.364
BrainStem_Core	D0.03cc[Gy]	44.0 ± 14.7	33.6 ± 15.1	<0.001 *	38.3 ± 17.0	28.6 ± 14.2	<0.001 *
BrainStem_Surf	D0.03cc[Gy]	43.0 ± 16.3	30.2 ± 16.4	<0.001 *	38.8 ± 19.3	28.5 ± 14.3	<0.001 *
OpticChiasm_PRV	D0.03cc[Gy]	31.7 ± 22.2	21.1 ± 20.6	<0.001 *	34.8 ± 20.6	22.0 ± 18.4	<0.001 *
OpticNerve_PRV	D0.03cc[Gy]	24.3 ± 25.6	20.0 ± 22.7	<0.001 *	22.0 ± 23.2	16.5 ± 19.7	0.002 *
Retina	D0.03cc[Gy]	7.4 ± 13.6	3.2 ± 8	<0.001 *	7.5 ± 12.8	3.3 ± 7.0	0.014 *
Brain	D5%[Gy]	71.4 ± 5.0	72.6 ± 4.6	0.013 *	73.2 ± 5.6	72.3 ± 5.3	0.059
Lens	D0.03cc[Gy]	1.2 ± 2.8	0.4 ± 1.5	0.027 *	1.7 ± 0.4	0.7 ± 0.3	0.689
HIPTV_7500		1.05 ± 0.01	1.06 ± 0.01	<0.001 *	1.06 ± 0.01	1.04 ± 0.02	<0.008 *
CIPTV_7500		0.80 ± 0.16	0.89 ± 0.07	0.002 *	0.68 ± 0.31	0.89 ± 0.08	0.003 *

The paired *t*-test was employed; asterisks (*) indicate a statistically significant difference between the submitted and KBP plan.

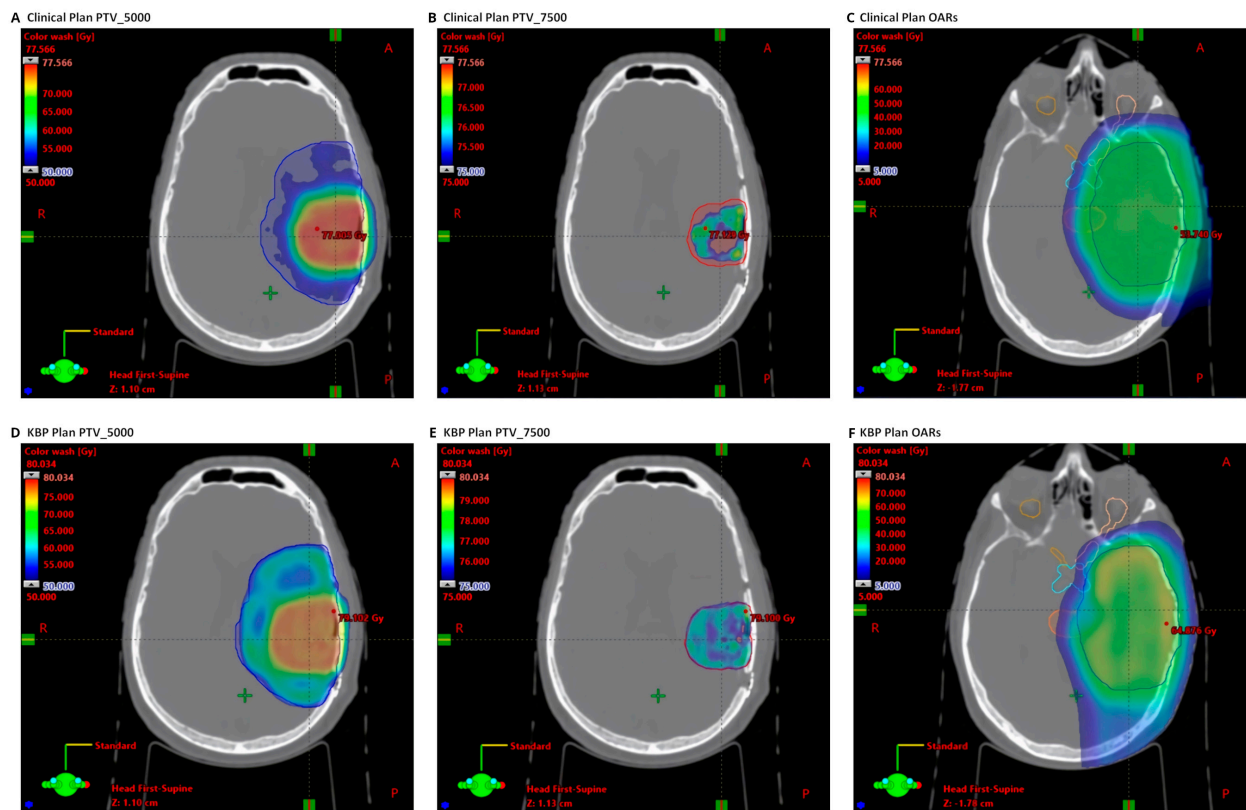


Figure 2. Dose distribution of an example proton therapy case. Panels (A–C) illustrate the dose distribution of the clinical plan, while panels (D–F) show the dose distribution of the KBP plan. The KBP plan demonstrates enhanced target coverage and reduced dose delivered to adjacent OARs, including the brainstem, optic chiasm_PRV, and left optic nerve_PRV.

3.3. NRG-HN001 Proton Plan Quality Review

In Table 5, the results from the IROC QA review of 20 proton therapy plans submitted to the NRG-HN001 are compared with KBP IMPT plans. The KBP IMPT plans demonstrated a notable improvement in compliance with the protocol criteria, with a reduction in the number of non-compliant cases by 54.8% and 75%, respectively.

Table 5. Comparison of IROC QA scores between the submitted NRG-HN001 proton plans and the KBP plans.

Structures	Dosimetric Parameter	Proton Submitted			Proton KBP		
		Score 1	Score 2	Score 3	Score 1	Score 2	Score 3
PTV_High	V100%[%]	3	4	13	13	4	3
PTV_High	D99%[%]	6	3	11	12	2	6
PTV_High	D0.03cc[%]	20	0	0	18	2	0
PTV_Intermediate1	V63Gy[%]/V62.7Gy[%]	2	0	7	8	1	0
PTV_Intermediate2	V59Gy[%]/V59.4Gy[%]	1	3	5	8	1	0
PTV_Low	V56Gy[%]	1	2	8	9	0	2
SpinalCord	D0.03cc[Gy]	18	2	0	20	0	0
BrainStem	D0.03cc[Gy]	13	7	0	20	0	0
OpticChiasm	D0.03cc[Gy]	17	1	0	20	0	0
OpticNerve_L	D0.03cc[Gy]	17	1	0	20	0	0
OpticNerve_R	D0.03cc[Gy]	17	1	0	20	0	0
TMjoint_L	D0.03cc[Gy]	15	0	0	15	0	0
TMjoint_R	D0.03cc[Gy]	15	0	0	15	0	0
Mandible	D0.03cc[Gy]	19	1	0	19	1	0
BrachialPlexus_L	D0.03cc[Gy]	18	2	0	20	0	0
BrachialPlexus_R	D0.03cc[Gy]	20	0	0	19	1	0
TemporalLobe_L	D0.03cc[Gy]	19	1	0	19	1	0
TemporalLobe_R	D0.03cc[Gy]	20	0	0	20	0	0
Parotid_L	Mean[Gy]	17	2	1	20	0	0
Parotid_R	Mean[Gy]	16	1	3	18	1	1

Score 1: per-protocol; Score 2: variation acceptable; Score 3: deviation unacceptable.

Table 6 presents an analysis of the average differences in critical dosimetric parameters between the submitted proton plans and the KBP IMPT plans. The analysis revealed that the KBP IMPT plans achieved a significant reduction in the maximum doses delivered to various critical structures. Specifically, reductions were observed in the brainstem (4.6 ± 6.8 Gy, $p = 0.008$), optic chiasm (8.9 ± 12 Gy, $p = 0.040$), left optic nerve (9.8 ± 10 Gy, $p = 0.034$), right optic nerve (13.1 ± 10 Gy, $p = 0.002$), left temporomandibular joint (4.6 ± 7.2 Gy, $p = 0.195$), right temporomandibular joint (5.6 ± 6.6 Gy, $p = 0.146$), left parotid gland (2.9 ± 5 Gy, $p = 0.040$), and right parotid gland (2.5 ± 4.7 Gy, $p = 0.067$).

Figure 3 provides a visual comparison of dose distribution in a typical case from the proton plan cohort. The KBP IMPT plans demonstrate superior target coverage and OAR sparing, although it is noteworthy that the KBP plan resulted in a higher maximum dose to the PTV and an increased volume receiving the prescription dose compared to the submitted clinical plan.

Table 6. Comparison of dosimetric parameters in submitted and KBP proton plans from HN001 clinical trial.

Structures	Dosimetric Parameter	Proton Submitted	Proton KBP	p Value
PTV_High	V100%[%]	42.1% ± 41.8%	84.1% ± 30.4%	<0.001 *
PTV_High	D99%[%]	89.7% ± 5.4%	93.3% ± 6.7%	0.037 *
PTV_High	D0.03cc[%]	102.2% ± 4.0%	111.0% ± 4.9%	<0.001 *
PTV_Intermediate1	V63Gy[%]/V62.7Gy[%]	53.3% ± 29.7%	97.1% ± 2.0%	<0.001 *
PTV_Intermediate2	V59Gy[%]/V59.4Gy[%]	77.3% ± 21.2%	97.1% ± 2.5%	<0.001 *
PTV_Low	V56Gy[%]	63.8% ± 24.7%	91.4% ± 15.0%	0.003 *
SpinalCord	D0.03cc[Gy]	37 ± 10.5	37.1 ± 2.3	0.486
BrainStem	D0.03cc[Gy]	51.3 ± 7.4	46.7 ± 2.9	0.008 *
OpticChiasm	D0.03cc[Gy]	34.3 ± 14.7	25.4 ± 15.7	0.040 *
OpticNerve_L	D0.03cc[Gy]	41.7 ± 14.3	31.9 ± 17.6	0.034 *
OpticNerve_R	D0.03cc[Gy]	42.7 ± 11.3	29.6 ± 15.2	0.002 *
TMjoint_L	D0.03cc[Gy]	52.5 ± 11.1	47.8 ± 16.4	0.195
TMjoint_R	D0.03cc[Gy]	50 ± 11.4	44.3 ± 16	0.146
Mandible	D0.03cc[Gy]	63.6 ± 6.7	64.3 ± 4.7	0.361
BrachialPlexus_L	D0.03cc[Gy]	60.9 ± 4.3	61.3 ± 2.3	0.345
BrachialPlexus_R	D0.03cc[Gy]	60.7 ± 3.6	61.6 ± 2.8	0.208
TemporalLobe_L	D0.03cc[Gy]	61.6 ± 6.8	60.7 ± 7.9	0.438
TemporalLobe_R	D0.03cc[Gy]	62.6 ± 6.2	62.3 ± 7.4	0.342
Parotid_L	Mean[Gy]	25.5 ± 6.3	22.6 ± 5.4	0.040 *
Parotid_R	Mean[Gy]	24.5 ± 5.3	22.1 ± 2.8	0.067
HIPTV_high		1 ± 0	1.1 ± 0	<0.001 *
CI PTV_High		0.3 ± 0.3	0.7 ± 0.3	<0.001 *

The paired *t*-test was employed; asterisks (*) indicate a statistically significant difference between the submitted and KBP plan.

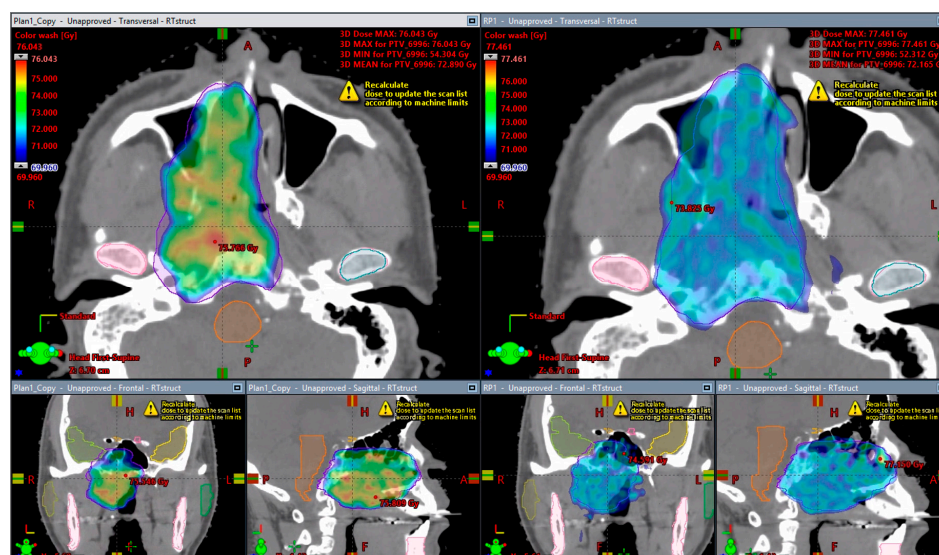


Figure 3. Dose distribution of an example case in the proton cohort of NRG-HN001. KBP IMPT plan (right) versus original submitted IMPT plan (left). KBP plan demonstrates enhanced target coverage and better sparing of the right temporal lobe.

4. Discussion

This investigation revealed more pronounced improvements in adherence to treatment protocols using the KBP model across both photon and proton modalities. The proton cohort showed notably superior dosimetric enhancements, with dose reductions ranging from 1.1 to 12.8 Gy, compared to the photon cohort, which observed improvements between 1.1 and 3.6 Gy. Although the examined photon plans displayed high quality—reflecting a mature development and implementation of IMRT techniques—the findings suggest there are still considerable opportunities for improvement through KBP. This could potentially refine treatment outcomes and increase adherence to established dosimetric guidelines.

The superior performance of KBP proton plans can be attributed to the use of specific advanced technologies, particularly the Varian Eclipse treatment planning system and the Varian ProBeam beam model. These results demonstrate that treatment outcomes can vary significantly depending on the technology and software used, as well as the level of expertise in treatment planning across different institutions. This study not only confirms the effectiveness of KBP in optimizing radiation therapy plans but also highlights the crucial role of technological and professional expertise in achieving optimal therapeutic outcomes. It emphasizes the need for continuous advancements in treatment planning tools and methodologies along with ongoing professional development and training for clinicians to fully harness the therapeutic potential of proton therapy.

Additionally, this study highlights the value of KBP tools as a robust benchmark for quality assurance in radiation therapy plans submitted for clinical trials. The future integration of KBP into the quality assurance processes of clinical trials could be pivotal, enhancing workflow efficiency and enabling a more thorough evaluation of treatment plans.

In this study, the evaluated proton plans submitted to NRG-BN001 incorporated both IMPT and PS plans. Between 2015 and 2016, a predominant majority (81%) of cases were treated with PS proton therapy, whereas this ratio decreased to 16% for patients enrolled between 2017 and 2019. In addition, the submitted IMPT plans had considerably superior dose conformity to the target than the submitted PS plans (CI PTV₇₅₀₀: 0.80 ± 0.16 vs. 0.68 ± 0.31). Despite the motion insensitivity of the PS system and less complex beam delivery [28], components such as scatter foils, range modulator wheel, and patient-specific compensator restrict beam conformity and limit maximum treatment depth [29]. In contrast, the pencil beam scanning (PBS) system uses magnets to manipulate the proton beam, enabling superior conformity, deeper treatment, and less neutron generation, as scattering foils and compensators are not required. The utilization of the PBS system, however, presents challenges such as increased complexity, longer delivery time, and low motion tolerance [30–32]. Consequently, while the passive scattering system was initially predominant, the pencil beam scanning approach is becoming progressively favored [32].

Recent studies have demonstrated the viability of using a KBP model for treatment plan QA and re-optimization [33–35]. The utilization of KBP has been shown to elevate planning efficiency and quality with reduced variability, thereby serving as a robust benchmark for clinical plans. The integration of these models within clinical trial QA processes not only enhances the overall quality but also has the potential to abbreviate the learning curve for clinical practitioners [14,25,36,37]. In our analysis, the application of these models has been particularly instrumental in evaluating the quality of treatment plans submitted to clinical trials, underscoring their utility as a critical assessment tool.

This study acknowledges several limitations. The constrained availability of proton plans necessitated the reliance on IMPT plans reconstituted from photon cases as surrogates for training the KBP proton models. This approach could introduce a potential bias into the training library, possibly affecting the model's quality. Moreover, the KBP models were constructed using IMPT plans derived from golden beam models provided by the system manufacturer, which might not align with the capabilities of equipment at participating institutions. Therefore, the plan quality depicted in this analysis represents what is attainable under ideal conditions with specific beam models and techniques, rather than a definitive representation of the variability in quality that might be encountered in real-world prac-

tice. Additionally, our premise is that improved plan quality could positively influence patient outcomes by reducing side effects and improving overall quality of life. However, it is important to note that as the clinical trials assessed in this study are still ongoing, we do not currently have access to the outcome data necessary to directly evaluate these potential benefits.

5. Conclusions

This investigation evaluated the quality of RT plans submitted to the multi-institutional clinical trials NRG-BN001 and NRG-HN001. It demonstrates the efficacy of KBP models in generating protocol-compliant plans and for RT plan QA. The findings indicate that the photon plans submitted to the NRG-BN001 clinical trial generally exhibit commendable quality. However, there is a marked variability in the quality of proton plans submitted for both NRG-BN001 and NRG-HN001, highlighting the emerging nature of this therapy. This study introduced the KBP-based models, which serve as a benchmark for the quality of plans that can be achieved in the management of tumors of the brain and head/neck region with radiation therapy. The KBP models built in this study will be published and made accessible to both the research and clinical communities for the purpose of RT plan QA and optimization.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cancers16112007/s1>, Table S1: NRG Oncology BN001 structure dosimetric compliance criteria; Table S2: NRG Oncology HN001 structure dosimetric compliance criteria; Table S3: NRG BN001 rapid plan model parameters. Table S4: NRG HN001 rapid plan proton model parameters.

Author Contributions: Conceptualization: H.G., Q.-T.L., N.Y.L., A.M.O., D.W., P.X. and Y.X. Methodology: T.L.C., H.G., N.Y.L., D.W. and Y.X. Software: T.L.C., D.W. and K.M. Validation: D.W. Formal analysis: D.W. Investigation: K.D.A., J.D.B., M.D.C., S.C., M.R.G., J.H., A.M.O., S.S., W.S., C.I.T., D.W. and Y.X. Resources: Y.C., M.R.G., M.P.M., J.M.M., A.M.O., C.I.T., D.W., Z.W. and Y.X. Data Curation: M.D.C., H.G., A.M.O. and D.W., Writing—Original Draft: D.W. Writing—Review and Editing: K.D.A., I.J.B., J.D.B., Y.C., M.D.C., T.L.C., S.C., H.G., M.R.G., V.G., J.H., Q.-T.L., N.Y.L., K.M., M.P.M., J.M.M., A.M.O., S.S., W.S., A.S., C.I.T., D.W., Z.W., P.X. and Y.X. Visualization: M.P.M. and D.W. Supervision: Y.X. Project Administration and Funding Acquisition: T.L.C. and Y.X. All authors have read and agreed to the published version of the manuscript.

Funding: This project was supported by NRG Oncology Network Group Operations Center and Imaging and Radiation Oncology Core (IROC) Group, grant number U10CA180868 and U24CA180803.

Institutional Review Board Statement: This study was in accordance with the Declaration of the NCI Central Institutional Review Board (NCI CIRB) and was approved by the Ethical Committee of NCI Community Oncology Research Program (NCORP) Ethics Board (NRG-BN001: Approval date 08/07/2014, NRG-HN001: Approval date 02/05/2014.). Sites participating with the NCI CIRB must obtain local IRB approval through NCI CIRB.

Informed Consent Statement: All patients who participated in the multi-center clinical trials signed fully informed consent forms provided in the trials. All patient data used in this study followed NCI patient deidentification guidelines.

Data Availability Statement: Third-party data: Restrictions apply to the availability of these data. Data were obtained from Imaging Oncology Core Radiotherapy Quality Assurance team. This is an ongoing trial; no data will be made available to the public before any publication of the endpoint of this trial. After the closure and publication of the endpoint of this trial, data can be requested via data sharing through NRG Oncology.

Acknowledgments: We would like to give thanks to Pekka Uusitalo and Reynald Vanderstraeten from Varian Medical Systems for providing the knowledge-based planning platform used in this study.

Conflicts of Interest: Drs Aldape, Battiste, Cao, Choi, Geng, Gondi, Men, Michalski, Sachdev, Wardak, and Mr Wang have declared they have no disclosures. Dr Barabi declares support to attend meetings or travel from BrainLab in the past 36 months. Dr Chan declares: in the past 36 months, Wake

Forest NCORP grant (UG CA189824-01) has funded 5% of my salary. I have received payment or honoraria from Monteris. I am a member of the Data Safety or Monitoring Board for Biomimetix. Dr Chenevert declares: since the initial planning of this work, subjects underwent magnetic resonance imaging (MRI) examinations as part of this study. I have research agreements with MRI vendors, GE, Siemens, and Philips with limited license fees paid to my institution. In the past 36 months, I have had an ongoing NIH-funded “Academic Industrial Partnership” with MRI vendors, GE, Siemens, and Philips related to MRI diffusion technology. I have received royalties or licenses from MRI vendors, GE, Siemens, and Philips. I have had limited license fees paid to my institution for institution-managed patented intellectual property, with me as co-inventor. Patents with me as co-inventor are assigned to and managed by the University of Michigan. MRI vendors, GE, Siemens, and Philips have licensed MRI technology-related IP. Dr Gilbert declares receipt of equipment, materials, drugs, medical writing, gifts, or other services from Chimerix and BMS (no payments, just drug supply) in the past 36 months. Dr Huang declares payment or honoraria from Baptist Health South Florida for CME and research support from Pfizer Inc and Cantex Inc for clinical trials in the past 36 months. Dr Le declares: in the past 36 months, NRG Oncology has paid for hotels and flights to NRG meetings. Dr Le is a leadership group chair (RTOGF) of NRG Oncology. Dr Lee declares consulting fees from Merck, Merck EMD, Galera, Yuming Consulting, Shanghai LTD, and Regeneron in the past 36 months. These were not involved with this paper and were support for attending meetings/travel from Varian. Dr Mehta declares consulting fees from Kazia, Mevion, Novocure, Telix, Zap and Xoft, leadership for Xcision, BDO—unpaid, stocks/options in Chimerix in the past 36 months. Dr Omuro declares consulting fees from Curevac, Ono Therapeutics, Pyramid, Telix, Nurix; participation in a data safety monitoring board or advisory board for Curevac in the past 36 months. Dr Shi declares consulting fees from Brainlab, Novocure, Varian, and Zai lab and advisory board payments from Novocure in the past 36 months. Dr Srinivasan declares consulting fees from GE Healthcare; payment or honoraria from Educational symposia Inc; leadership or fiduciary role in the American Society of Head and Neck Radiology and Western Neuroradiological Society in the past 36 months. Dr Tsien declares consulting fees from Novocure; payment or honoraria from Varian and Novocure; support for attending meetings and/or travel from Zeiss; participation in a data safety monitoring board or advisory board from Novocure in the past 36 months. Dr Xia declares grants/contracts from AVO and Varian Raysearch workstation for testing purposes in the past 36 months. Dr Xiao declares grants from 2U24CA180803-06 (IROC) and 2U10CA180868-06 (NRG) since the initial planning of this work.

References

1. Young, R.M.; Jamshidi, A.; Davis, G.; Sherman, J.H. Current Trends in the Surgical Management and Treatment of Adult Glioblastoma. *Ann. Transl. Med.* **2015**, *3*, 121. [[PubMed](#)]
2. Ostrom, Q.T.; Gittleman, H.; Farah, P.; Ondracek, A.; Chen, Y.; Wolinsky, Y.; Stroup, N.E.; Kruchko, C.; Barnholtz-Sloan, J.S. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2006–2010. *Neuro Oncol.* **2013**, *15* (Suppl. S2), ii1–ii56. [[CrossRef](#)]
3. Noch, E.K.; Ramakrishna, R.; Magge, R. Challenges in the Treatment of Glioblastoma: Multisystem Mechanisms of Therapeutic Resistance. *World Neurosurg.* **2018**, *116*, 505–517. [[CrossRef](#)] [[PubMed](#)]
4. Stupp, R.; Mason, W.P.; van den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M.J.B.; Belanger, K.; Brandes, A.A.; Marosi, C.; Bogdahn, U.; et al. Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N. Engl. J. Med.* **2005**, *352*, 987–996. [[CrossRef](#)] [[PubMed](#)]
5. Stupp, R.; Taillibert, S.; Kanner, A.; Read, W.; Steinberg, D.M.; Lhermitte, B.; Toms, S.; Idbaih, A.; Ahluwalia, M.S.; Fink, K.; et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide Vs Maintenance Temozolomide Alone on Survival in Patients with Glioblastoma. *JAMA* **2017**, *318*, 2306–2316. [[CrossRef](#)] [[PubMed](#)]
6. Armocida, D.; Pesce, A.; Di Giammarco, F.; Frati, A.; Santoro, A.; Salvati, M. Long Term Survival in Patients Suffering from Glioblastoma Multiforme: A Single-Center Observational Cohort Study. *Diagnostics* **2019**, *9*, 209. [[CrossRef](#)] [[PubMed](#)]
7. Wu, L.; Li, C.; Pan, L. Nasopharyngeal Carcinoma: A Review of Current Updates. *Exp. Ther. Med.* **2018**, *15*, 3687–3692. [[CrossRef](#)] [[PubMed](#)]
8. Figen, M.; Çolpan Öksüz, D.; Duman, E.; Prestwich, R.; Dyker, K.; Cardale, K.; Ramasamy, S.; Murray, P.; Şen, M. Radiotherapy for Head and Neck Cancer: Evaluation of Triggered Adaptive Replanning in Routine Practice. *Front. Oncol.* **2020**, *10*, 579917. [[CrossRef](#)] [[PubMed](#)]
9. Abrams, R.A.; Winter, K.A.; Regine, W.F.; Safran, H.; Hoffman, J.P.; Lustig, R.; Konski, A.A.; Benson, A.B.; Macdonald, J.S.; Rich, T.A.; et al. Failure to Adhere to Protocol Specified Radiation Therapy Guidelines was Associated with Decreased Survival in RTOG 9704—A Phase III Trial of Adjuvant Chemotherapy and Chemoradiotherapy for Patients with Resected Adenocarcinoma of the Pancreas. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *82*, 809–816. [[CrossRef](#)]

10. Gwynne, S.; Spezi, E.; Sebag-Montefiore, D.; Mukherjee, S.; Miles, E.; Conibear, J.; Staffurth, J. Improving Radiotherapy Quality Assurance in Clinical Trials: Assessment of Target Volume Delineation of the Pre-Accrual Benchmark Case. *Br. J. Radiol.* **2013**, *86*, 20120398. [[CrossRef](#)]
11. Peters, L.J.; O'Sullivan, B.; Giralt, J.; Fitzgerald, T.J.; Trotti, A.; Bernier, J.; Bourhis, J.; Yuen, K.; Fisher, R.; Rischin, D. Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results from TROG 02.02. *J. Clin. Oncol.* **2010**, *28*, 2996–3001. [[CrossRef](#)]
12. Powis, R.; Bird, A.; Brennan, M.; Hinks, S.; Newman, H.; Reed, K.; Sage, J.; Webster, G. Clinical Implementation of a Knowledge Based Planning Tool for Prostate VMAT. *Radiat. Oncol.* **2017**, *12*, 81. [[CrossRef](#)]
13. Wu, H.; Jiang, F.; Yue, H.; Zhang, H.; Wang, K.; Zhang, Y. Applying a RapidPlan Model Trained on a Technique and Orientation to another: A Feasibility and Dosimetric Evaluation. *Radiat. Oncol.* **2016**, *11*, 108. [[CrossRef](#)]
14. Ge, Y.; Wu, Q.J. Knowledge-Based Planning for Intensity-Modulated Radiation Therapy: A Review of Data-Driven Approaches. *Med. Phys.* **2019**, *46*, 2760–2775. [[CrossRef](#)]
15. Good, D.; Lo, J.; Lee, W.R.; Wu, Q.J.; Yin, F.; Das, S.K. A Knowledge-Based Approach to Improving and Homogenizing Intensity Modulated Radiation Therapy Planning Quality among Treatment Centers: An Example Application to Prostate Cancer Planning. *Int. J. Radiat. Oncol. Biol. Phys.* **2013**, *87*, 176–181. [[CrossRef](#)]
16. Giaddui, T.; Chen, W.; Yu, J.; Lin, L.; Simone, C.B.; Yuan, L.; Gong, Y.U.T.; Wu, Q.J.; Mohan, R.; Zhang, X.; et al. Establishing the Feasibility of the Dosimetric Compliance Criteria of RTOG 1308: Phase III Randomized Trial Comparing overall Survival After Photon Versus Proton Radiochemotherapy for Inoperable Stage II-IIIb NSCLC. *Radiat. Oncol.* **2016**, *11*, 66. [[CrossRef](#)]
17. Younge, K.C.; Marsh, R.B.; Owen, D.; Geng, H.; Xiao, Y.; Spratt, D.E.; Foy, J.; Suresh, K.; Wu, Q.J.; Yin, F.; et al. Improving Quality and Consistency in NRG Oncology Radiation Therapy Oncology Group 0631 for Spine Radiosurgery Via Knowledge-Based Planning. *Int. J. Radiat. Oncol. Biol. Phys.* **2018**, *100*, 1067–1074. [[CrossRef](#)]
18. Zhu, X.; Ge, Y.; Li, T.; Thongphiew, D.; Yin, F.; Wu, Q.J. A Planning Quality Evaluation Tool for Prostate Adaptive IMRT Based on Machine Learning. *Med. Phys.* **2011**, *38*, 719–726. [[CrossRef](#)]
19. Moore, K.L.; Brame, R.S.; Low, D.A.; Mutic, S. Experience-Based Quality Control of Clinical Intensity-Modulated Radiotherapy Planning. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *81*, 545–551. [[CrossRef](#)]
20. Giaddui, T.; Geng, H.; Chen, Q.; Linnemann, N.; Radden, M.; Lee, N.Y.; Xia, P.; Xiao, Y. Offline Quality Assurance for Intensity Modulated Radiation Therapy Treatment Plans for NRG-HN001 Head and Neck Clinical Trial using Knowledge-Based Planning. *Adv. Radiat. Oncol.* **2020**, *5*, 1342–1349. [[CrossRef](#)]
21. Wu, B.; McNutt, T.; Zahurak, M.; Simari, P.; Pang, D.; Taylor, R.; Sanguineti, G. Fully Automated Simultaneous Integrated Boosted-Intensity Modulated Radiation Therapy Treatment Planning is Feasible for Head-and-Neck Cancer: A Prospective Clinical Study. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *84*, 647. [[CrossRef](#)]
22. Chen, H.; Craft, D.L.; Gierga, D.P. Multicriteria Optimization Informed VMAT Planning. *Med. Dosim.* **2014**, *39*, 64–73. [[CrossRef](#)]
23. Geng, H.; Giaddui, T.; Cheng, C.; Zhong, H.; Ryu, S.; Liao, Z.; Yin, F.; Gillin, M.; Mohan, R.; Xiao, Y. A Comparison of Two Methodologies for Radiotherapy Treatment Plan Optimization and QA for Clinical Trials. *J. Appl. Clin. Med. Phys.* **2021**, *22*, 329–337. [[CrossRef](#)]
24. Cao, W.; Gronberg, M.; Olanrewaju, A.; Whitaker, T.; Hoffman, K.; Cardenas, C.; Garden, A.; Skinner, H.; Beadle, B.; Court, L. Knowledge-based Planning for the Radiation Therapy Treatment Plan Quality Assurance for Patients with Head and Neck Cancer. *J. Appl. Clin. Med. Phys.* **2022**, *23*, e13614. [[CrossRef](#)]
25. Fogliata, A.; Wang, P.; Belosi, F.; Clivio, A.; Nicolini, G.; Vanetti, E.; Cozzi, L. Assessment of a Model Based Optimization Engine for Volumetric Modulated Arc Therapy for Patients with Advanced Hepatocellular Cancer. *Radiat. Oncol.* **2014**, *9*, 236. [[CrossRef](#)]
26. Paddick, I. A Simple Scoring Ratio to Index the Conformity of Radiosurgical Treatment Plans. Technical Note. *J. Neurosurg.* **2000**, *93* (Suppl. S3), 219–222. [[CrossRef](#)]
27. van't Riet, A.; Mak, A.C.; Moerland, M.A.; Elders, L.H.; van der Zee, W. A Conformation Number to Quantify the Degree of Conformality in Brachytherapy and External Beam Irradiation: Application to the Prostate. *Int. J. Radiat. Oncol. Biol. Phys.* **1997**, *37*, 731–736. [[CrossRef](#)]
28. Langen, K.; Zhu, M. Concepts of PTV and Robustness in Passively Scattered and Pencil Beam Scanning Proton Therapy. *Semin. Radiat. Oncol.* **2018**, *28*, 248–255. [[CrossRef](#)]
29. Liu, H.; Chang, J.Y. Proton Therapy in Clinical Practice. *Chin. J. Cancer* **2011**, *30*, 315–326. [[CrossRef](#)]
30. Kanai, T.; Kawachi, K.; Kumamoto, Y.; Ogawa, H.; Yamada, T.; Matsuzawa, H.; Inada, T. Spot Scanning System for Proton Radiotherapy. *Med. Phys.* **1980**, *7*, 365–369. [[CrossRef](#)]
31. Seco, J.; Robertson, D.; Trofimov, A.; Paganetti, H. Breathing Interplay Effects during Proton Beam Scanning: Simulation and Statistical Analysis. *Phys. Med. Biol.* **2009**, *54*, 283. [[CrossRef](#)] [[PubMed](#)]
32. Yoo, G.S.; Yu, J.I.; Cho, S.; Jung, S.H.; Han, Y.; Park, S.; Oh, Y.; Lee, B.; Park, H.C.; Lim, D.H.; et al. Comparison of Clinical Outcomes between Passive Scattering Versus Pencil-Beam Scanning Proton Beam Therapy for Hepatocellular Carcinoma. *Radiother. Oncol.* **2020**, *146*, 187–193. [[CrossRef](#)] [[PubMed](#)]
33. Delaney, A.R.; Verbakel, W.F.; Lindberg, J.; Koponen, T.K.; Slotman, B.J.; Dahele, M. Evaluation of an Automated Proton Planning Solution. *Cureus* **2018**, *10*, e3696. [[CrossRef](#)] [[PubMed](#)]

34. Tol, J.P.; Dahele, M.; Delaney, A.R.; Slotman, B.J.; Verbakel, W.F.A.R. Can Knowledge-Based DVH Predictions be used for Automated, Individualized Quality Assurance of Radiotherapy Treatment Plans? *Radiat. Oncol.* **2015**, *10*, 234. [[CrossRef](#)] [[PubMed](#)]
35. Liao, Z.; Lee, J.J.; Komaki, R.; Gomez, D.R.; O'Reilly, M.S.; Fossella, F.V.; Blumenschein, G.R.; Heymach, J.V.; Vaporciyan, A.A.; Swisher, S.G.; et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* **2018**, *36*, 1813–1822. [[CrossRef](#)]
36. Fogliata, A.; Belosi, F.; Clivio, A.; Navarria, P.; Nicolini, G.; Scorsetti, M.; Vanetti, E.; Cozzi, L. On the Pre-Clinical Validation of a Commercial Model-Based Optimisation Engine: Application to Volumetric Modulated Arc Therapy for Patients with Lung Or Prostate Cancer. *Radiother. Oncol.* **2014**, *113*, 385–391. [[CrossRef](#)]
37. Li, N.; Carmona, R.; Sirak, I.; Kasaova, L.; Followill, D.; Michalski, J.; Bosch, W.; Straube, W.; Mell, L.K.; Moore, K.L. Highly Efficient Training, Refinement, and Validation of a Knowledge-Based Planning Quality-Control System for Radiation Therapy Clinical Trials. *Int. J. Radiat. Oncol. Biol. Phys.* **2017**, *97*, 164–172. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.