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Original Research Article

Knowledge-based automatic plan optimization for left-sided whole breast tomotherapy

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ABSTRACT

Background/Purpose: Tomotherapy may deliver high-quality whole breast irradiation at static angles. The aim of this study was to implement Knowledge-Based (KB) automatic planning for left-sided whole breast using this modality.

Materials/Methods: Virtual volumetric plans were associated to the dose distributions of 69 Tomotherapy (TT) clinical plans of previously treated patients, aiming to train a KB-model using a commercial tool completely implemented in our treatment planning system. An individually optimized template based on the resulting KB-model was generated for automatic plan optimization. Thirty patients of the training set and ten new patients were considered for internal/external validation. Fully-automatic plans (KB-TT) were generated and compared using the same geometry/number of fields of the corresponding clinical plans.

Results: KB-TT plans were successfully generated in 26/30 and 10/10 patients of the internal/external validation sets; for 4 patients whose original plans used only two fields, the manual insertion of one/two fields before running the automatic template was sufficient to obtain acceptable plans. Concerning internal validation, planning target volume $V_{95\%}/D_{1\%}$/dose distribution standard deviation improved by 0.9%/0.4Gy/0.2Gy ($p < 0.05$) against clinical plans; Organs at risk mean doses were also slightly improved ($p < 0.05$) by 0.07/0.4/0.2/0.01 Gy for left lung/heart/right breast/right lung respectively. Similarly satisfactory results were replicated in the external validation set. The resulting treatment duration was 8 ± 1 min, consistent with our clinical experience. The active planner time per patient was 5–10 minutes.

Conclusion: Automatic TT left-sided breast KB-plans are comparable to or slightly better than clinical plans and can be obtained with limited planner time. The approach is currently under clinical implementation.

1. Introduction

Breast-conserving surgery coupled with Whole Breast Irradiation (WBI) allows a reduction of the absolute risk of cancer relapse [1,2]. The conventional fractionation protocols consisted in delivering 50 Gy in 25 fractions. Different hypofractionated protocols have recently been introduced delivering the treatment in 5–20 fractions [3,4]; among them, moderate hypofractionation delivering 40 Gy in 15 fractions (or 42.5 Gy in 16 fractions), still represents the gold standard for many Institutes [4]. Despite the evolution toward increasing the dose to the tumor bed (Simultaneous Integrated Boost) or including the nodal region in the target for selected categories of patients [5–8], WBI remains one of the most used breast cancer radiotherapy approaches.

The most used techniques for WBI consist in the delivery of tangential fields, applying different techniques: 3-Dimensional Conformal RadioTherapy (3DCRT) with both physical and dynamic wedges; Intensity Modulated RadioTherapy (IMRT) usually obtained with 2 to 4 segments per beam, manually optimized (Field in Field) with a conventional Linac, or inversely optimized by conventional Linac or delivered using a tomotherapy system in static angles modality. These techniques allow a reduction of the low dose spread to Organs-At-Risk (OARs) and Body, thanks to the selected beam geometry [9–14].

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The optimization process is time consuming, and the quality of the resulting plan is highly dependent on the planner's experience. [15] For a certain institute, one way to increase plan homogeneity is to standardize the radiotherapy treatment, with the aim of guaranteeing a high quality plan for all patients, regardless of time availability and user skills. [16] Automatic planning approaches have a key role in this scenario, helping to reach an optimal plan, reducing planning time and limiting/avoiding intra-operator variability [17–20].

Many groups have investigated various auto-planning approaches for different clinical applications, including breast site [21–26]. Tangential-Field (TF) geometry presents certain difficulties considering the degree to which inter-patient variability influences the choice of optimal field angles. A suboptimal selection of the segment position is highly correlated to a suboptimal plan with a consequent increase in the dose delivered to OARs.

Nonetheless, many automatic solutions employing various approaches have been proposed: in-house solutions [15,24,27] or commercially available systems [28,29,23], among which it is possible to find a tool using a Knowledge-Based (KB) approach. Due to the large number of WBI patients, KB is expected to be a good candidate method to reach an automation process for the breast site [21,22]. We have previously demonstrated the capability of KB to predict TF-geometry dose distribution [30], given its ability to completely replace manual planning with WBI in the context of TF delivered with 3DCRT. On the other hand, KB applications for TomoTherapy (TT) environment have already been reported, although in a different site (i.e. prostate cancer) [31,32]. The principal goals of this study were to train a prediction model for the static angles modality on a TT system to be applied to left-sided WBI. Moreover, using this prediction model we aimed to automatize plan optimization, replacing manual planning, eliminating suboptimal plans and reducing both inter-operator variability and planning time.

2. Materials and methods

2.1. Treatment protocol

A set of 79 left-sided breast cancer patients treated with tomotherapy at our Institute in the period 2017–2021 were available. They were treated delivering 40 Gy in 15 fractions (2.67 Gy/fr), prescribed as median dose to PTV (Planning Target Volume). Patients were set in a supine position, immobilized using a Posiboard™ or Wing Board™ (CIVICO, Inc.) breast immobilizer. Arms were positioned above the head to avoid inclusion in the field. CTV (Clinical Target Volume), PTV and OARs were delineated following the (AIRO) national guidelines: CTV was cropped with respect to the body with a 5 mm margin to exclude skin; PTV was obtained by expanding the CTV isotropically by 5 mm, and cropped analogously to CTV.

The treatment machine was a TomoHD™ (v. 2.1.4) system used in TomoDirect™ (static angles) modality, delivering 6 MV Flattening Filter Free beams, coupled with the v.5.1.1.6 Planning Station. When setting up the fields, the MLC (MultiLeaf Collimator) leaves were opened to the air by the system's skin flash tool in order to take account of intra- and inter-fraction movements or deformations, assuring a distance between body and MLC projection of approximately 3 cm when allowed by the geometry.

The distribution of the parameters used in the planning process as well as the plan acceptability parameters are shown in the supplementary materials: Tables s1 and s2 respectively. This study was approved by the Ethical Committee of our institution (protocol number 248/2021).

2.2. Model Generation

The model generation took place in the Treatment Planning System (TPS) Eclipse™ from Varian Medical System, Inc. This TPS includes a commercially available tool called RapidPlan (RP) that exploits the KB approach. Three different sets of data were extracted by RP from previous clinical plans: beam geometry, patient contours and dose distribution. Using Principal Component Analysis, RP generated a regression model correlating geometrical information (patient anatomy) to the Dose-Volume Histogram (DVH), considering the beam arrangement used for the specific plan [33,34]. To do so, RP required an inverse-planned modality plan as input in the training phase. For this reason, mock rotational VMAT (Volumetric Modulated Arc Therapy) plans were generated using the geometry arrangement of the ViTAT (Virtual Tangential-fields Arc Therapy) technique introduced in previous works [30,35]. In short, four arcs were used, ranging from 300° to 135°, with collimator angles equal to ±5° and ±10°. Mock plans were obtained using a plan template that automatically generated the beam arrangements and properties. No optimization was required at this phase. Dose distributions of TT plans were exported from the TT system and imported in Eclipse™ to be linked to the corresponding mock ViTAT plan. The so generated mock plan was then used in the training set of the RP model. Only 79 patients were available, 69 of which were used to train a KB regression model. The OARs considered in the model were heart, ipsilateral lung, contralateral lung and contralateral breast.

2.3. Outlier removal andtemplate optimization

In order to assure that the training set used for the model contained only high quality plans, an outlier exclusion process was followed using the tools inside the RP and the Varian tool Model Analytics.

Given a regression diagram (Fig. s1 in Supplementary materials) with the standard deviation σ of the model, an outlier is first recognized as a point distant from the linear trend by a value higher than 2 σ. As previously explained [33] there were two types of outliers: geometrical and dosimetric. The former are associated with an uncommon anatomical feature and were maintained in the model, while the latter are associated with suboptimal plans and were therefore excluded.

For each OAR, RP generates a prediction band that indicates where the DVH for a new patient is most likely to 'land'. From these bands it is possible to generate a template, but the position and priorities of the objectives must be carefully selected.

The TT template distinguished the structures in targets and OARs: for the PTV, a maximum dose constraint was used along with one DVH point expressed as the median prescribed dose. For the OARs, a maximum dose constraint was used and only three other DVH points may be selected; each constraint was linked to a penalty coefficient. Moreover, each structure was associated with an 'importance' parameter that allows the plan to be optimized for the whole structure, rather than for only a single DVH point.

The template was iteratively optimized and modified on a set of 5 patients, until an optimal plan was obtained for all five patients. Structure importance, constraint penalties, maximum dose for OARs, and maximum and minimum dose for the target were all optimized.

The template was generated in the Varian TPS and translated into an executable TT template using the Eclipse Scripting Application Programming Interface (ESAPI).

Subsequently, it was automatically sent to the TT Planning Station, to be used in the optimization process (Fig. s2 in Supplementary Materials).

In the template, a control structure called "Shell" was used. It was generated by expanding the PTV isotropically by a margin of 3 cm, and furthermore expanding the thus generated Shell by a 5 cm margin in the postero-lateral direction, but only in the body region in correspondence to the distal beam. The Shell was then cropped with 0 mm margin with respect to PTV, contralateral breast, lungs, heart and body (Fig. s3 in Supplementary Materials). The shell allows an increase in the conformity of the PTV dose distribution. The optimization calculation grid was set to "fine" (corresponding to 1.95 mm × 1.95 mm) to better control the presence of hot spots of high dose inside and outside the target.

2.4. Model Validation

Model performances were evaluated by means of both an internal and external validation process: 30 out of the 69 patients used for training, were randomly chosen for the internal validation, while the remaining 10 out of 79 new patients were considered for the external validation.

The fully automatic optimized plans (KB-TT), obtained following the workflow described in Fig. s2 in Supplementary Materials, were compared with the clinical ones.

In order to compare plans considering only the change in the optimization modality, the same beam arrangements of clinical TT plans were used for KB-TT plans. The comparison between KB-TT and TT plans was carried out in terms of dose-volume parameters: for the PTV, $V_{95\%}$, $D_{1\%}$, $D_{2\%}$ and the standard deviation of PTV dose distribution (used as homogeneity index) were considered; for OARs, $D_{2\%}$ and mean dose were used. The standard deviation of the PTV dose is used as a target dose-homogeneity metric.

The characteristics of planning parameters used for TT clinical plans for the validation tests are shown in the Supplementary Materials.

The field width was set to 2.5 cm, used for the template tests and for the validation tests, along with a modulation factor of 2.000 and a pitch of 0.251. These parameters were fixed for all automatic planning optimization. The distribution of clinical values for these parameters showed the necessity of increasing the modulation for some specific plans (35%). The parameter values associated with a higher modulation were used for all patients in order to guarantee a wider applicability. Paired sample Wilcoxon tests were performed to assess significance of results.

3. Results

The KB-TT model was generated excluding the dosimetric outliers: in total 9 patients were outliers for at least one OAR, resulting in a number of trained patients between 62 and 66 for the different OARs. R^2 values were equal to or higher than 0.70 for all structures except the contralateral breast (see Tables s3 and Fig. s1 in supplementary materials). The final optimized template is shown in Table 1.

The 30 automatic plans obtained for the internal validation set were all acceptable apart from four that were found to be unacceptable in terms of PTV coverage. Overall, KB-TT plans showed small but significant ($p < 0.05$) improvement in the internal validation set (Table 2 and Fig. 1): better PTV $V_{95\%}$ (0.9%), improved PTV $D_{1\%}$ (0.4 Gy) and standard deviation of PTV dose (0.2 Gy); Ipsilateral Lung and Heart received a lower mean dose by 0.07 Gy and 0.4 Gy; mean dose to contralateral OARs was reduced by at least 4.8% relative to the clinical TT; integral dose to body was reduced by 0.3 Gy. Delivery time for KB-TT plans averaged over all 30 patients was 8 ± 1 min that is comparable with the delivery time resulting from clinical plans delivered using 5 cm fields (6 ± 1 min) and 2.5 cm fields (8 ± 2 min).

The same trend was found for the external validation set, but the significance of the obtained value was not found: KB-TT plans resulted in similar PTV coverage, better PTV D1% (0.5 Gy, $p < 0.05$) and slightly better PTV homogeneity. There was a reduction of 0.4 Gy and 0.1 Gy to D2% of ipsilateral lung and contralateral breast, respectively (Table 3 and Fig. 2).

The delivery time for KB-TT plans averaged over the entire 10 patient population was 8 ± 1 min against 6 ± 1 min and 9 ± 1 min for the 5 cm and the 2.5 cm field clinical plans respectively.

Table 1
TT fine-tuned optimization template. Structure priority is shown in parentheses before organ name. PTV is treated as the target (T) structure and prescription is normalized to the median of organ dose. "Gen." placeholder is automatically replaced with the corresponding value exported from RP prediction.

Fine-Tuned Optimization Template						
(Priority) Organ	*Importance*	*D_{max} [Gy]*	*D_{max} Penalty*	*Vol. [%]*	*Dose [Gy]*	*Penalty*
(T) **PTV**	20	40	55	Median	40	55
(1) **Heart**	4	40	15	Gen.	5	12
				Gen.	16	16
				Gen.	30	15
(2) **Contr. Breast**	3	Gen.	30	Gen.	1	30
(3) **Ipsi. Lung**	4	40	10	Gen.	5	20
				Gen.	20	20
				Gen.	30	12
(4) **Contr. Lung**	2	Gen.	30	Gen.	1	5
(5) **Shell**	5	40	70	7	38	7

Table 2
Quantitative comparison between KB-TT and TT plans for the Internal Validation set. Median values for each set are shown along with the interquartile range (in brackets). Bold font is associated with significant ($p < 0.05$) results. SD is the standard deviation of the PTV dose distribution, it is used as homogeneity index.

Internal Validation				
Organ	*Parameter*	*TT*	*KB-TT*	*ΔP*
PTV	$V_{95\%}$ [%]	97.5 [1.9]	98.4 [1.5]	**−0.9**
	$D_{2\%}$ [Gy]	41.0 [0.3]	40.6 [0.3]	**0.4**
	$D_{1\%}$ [Gy]	41.2 [0.4]	40.8 [0.3]	**0.4**
	SD [Gy]	0.8 [0.3]	0.6 [0.2]	**0.2**
Body	D_{mean} [Gy]	3.5 [1.3]	3.2 [1.1]	**0.3**
	$D_{2\%}$ [Gy]	39.9 [0.2]	39.8 [0.2]	**0.1**
Heart	V_{3Gy} [%]	10.1 [8.6]	7.7 [4.8]	**2.4**
	V_{16Gy} [%]	2.4 [2.7]	1.9 [1.6]	0.1
	D_{mean} [Gy]	1.9 [1.1]	1.5 [0.9]	**0.4**
	$D_{2\%}$ [Gy]	18.5 [15.9]	15.4 [8.6]	3.1
Contralateral Lung	D_{mean} [Gy]	0.21 [0.08]	0.20 [0.06]	**0.01**
	$D_{2\%}$ [Gy]	0.6 [0.2]	0.6 [0.1]	**0.00**
Contralateral Breast	D_{mean} [Gy]	0.27 [0.13]	0.24 [0.05]	**0.03**
	$D_{2\%}$ [Gy]	0.9 [0.5]	0.7 [0.3]	**0.2**
Ipsilateral Lung	V_{5Gy} [%]	22.0 [5.2]	21.5 [4.3]	0.5
	V_{20Gy} [%]	11.3 [3.1]	11.0 [4.0]	**0.3**
	D_{mean} [Gy]	5.43 [1.1]	5.36 [1.4]	**0.07**
	$D_{2\%}$ [Gy]	37.5 [1.1]	36.7 [1.8]	**0.8**

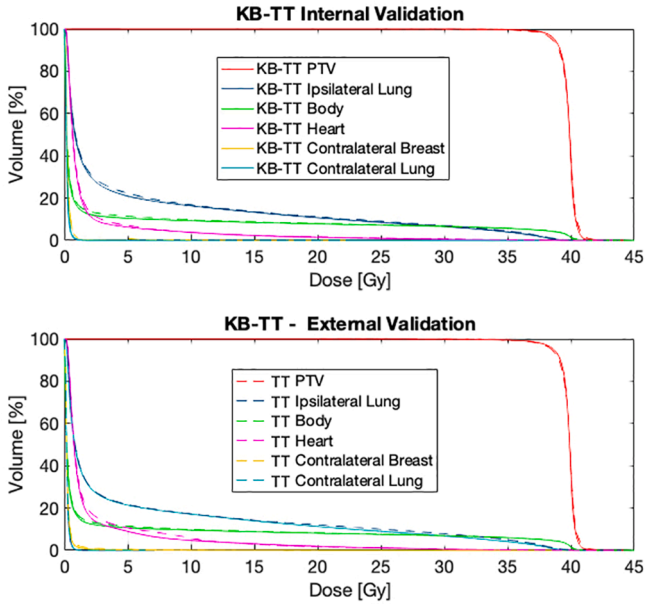

Fig. 1. Mean DVH comparison between KB-TT and TT plans, for both internal (top) and external (bottom) validation sets. KB-TT is associated with a solid line, and TT with dashed line.

Table 3
Quantitative comparison between KB-TT and TT plans for the External Validation set. Median values of each set are shown along with the interquartile range (in brackets). Bold font is associated with significant ($p < 0.05$) results. SD is the standard daviation of the PTV dose distribution, it is used as a homogeneity index.

External Validation				
Organ	*Parameter*	*TT*	*KB-TT*	*ΔP*
PTV	$V_{95\%}$ [%]	96.9 [1.2]	97.8 [1.5]	−0.9
	$D_{2\%}$ [Gy]	41.1 [0.5]	40.7 [0.2]	**0.4**
	$D_{1\%}$ [Gy]	41.3 [0.7]	40.8 [0.3]	**0.5**
	SD [Gy]	0.9 [0.3]	0.7 [0.3]	**0.2**
Body	D_{mean} [Gy]	3.4 [1.0]	3.2 [0.9]	0.2
	$D_{2\%}$ [Gy]	39.8 [0.2]	39.8 [0.1]	0.0
Heart	V_{3Gy} [%]	12.8 [10.0]	9.9 [8.5]	2.9
	V_{16Gy} [%]	2.4 [1.2]	2.5 [1.9]	−0.1
	D_{mean} [Gy]	2.3 [0.9]	1.9 [0.9]	0.4
	$D_{2\%}$ [Gy]	16.8 [5.5]	18.0 [7.9]	−1.2
Contralateral Lung	D_{mean} [Gy]	0.21 [0.08]	0.20 [0.04]	0.01
	D_2 [Gy]	0.55 [0.10]	0.50 [0.11]	0.05
Contralateral Breast	D_{mean} [Gy]	0.26 [0.11]	0.23 [0.13]	0.03
	$D_{2\%}$ [Gy]	0.8 [1.4]	0.7 [1.2]	**0.1**
Ipsilateral Lung	V_{5Gy} [%]	21.9 [4.6]	21.2 [2.1]	0.7
	V_{20Gy} [%]	12.2 [1.8]	11.4 [1.5]	**0.8**
	D_{mean} [Gy]	5.6 [0.8]	5.3 [0.6]	**0.3**
	$D_{2\%}$ [Gy]	37.9 [0.8]	37.5 [0.9]	0.4

4. Discussion

We proposed an approach using a commercially available system to automate the plan optimization process for WBI, using RP to handle dose distributions not delivered through its native TPS environment, obtaining equal to or slightly better plans in terms of PTV coverage ($V_{95\%}$), mean OAR doses and dose-volume parameters in general.

The quality of the obtained plan is in line with other authors findings for KB models [23,35,36].

Previous examples [31,32] show the feasibility of using RP for different environments. The translation of the DVH prediction band into an effective, individually optimized fine-tuned template, as a first step, and the following translation of the native TPS template into a TT executable one are a fundamental step of this work.

In principle, the translation step could be carried out manually without the use of the script, making the implementation of this process clinically possible in all centers that have a TT system and the RP software available. The use of the script, however, allows the possibility of speeding up the process and simplifying the use of this methodology being implemented inside the TPS used in daily clinical procedures.

While generating the model, a field geometry had to be established. For this reason we used the ViTAT geometry even though it is not directly referred to the original clinical plan, because, as previously found [30,37], it is possible to link the dose distribution obtained with tangential field arrangement to a mock rotational plan. The mock geometry is easily and rapidly obtainable by setting an appropriate plan setup template in the native TPS environment.

Moreover, the model regression plots were optimal for breast application as confirmed by the obtained results. The contralateral breast is associated to the lower value since this organ is not always visible from the beam's-eye-views, and it is consequently more difficult for the system to associate the geometric component to the dosimetric one.

It is important to notice that user personalization is limited due to the use of a protocol with fixed field width, pitch and modulation factors. Only four plans out of thirty were found to be unacceptable; in fact they were associated with the use of only two fields. Adding other two segments to a total of four (modifying the entrance angle by 5° from the clinical ones) and re-starting the automatic optimization, it was possible to obtain acceptable plans, with better PTV coverage compared to the original clinical ones (Fig. 2).

The use of four beams allowed the generation of the totality of acceptable plans; it is therefore suggested always to select four segments, instead of just two, in order to increase coverage and modulation. The dimension of the internal validation cohort was sufficiently high to highlight the significant differences; unfortunately, due to the small number of patients included in the set, only 10 patients were available for the external validation cohort at the time of the present study.

Due to the small number of patients, the significance of the reported differences, with respect to the internal validation case, was lost; however, the results showed a pattern very similar to that found in the internal set. When possible, by increasing the number of patients in the external validation set, it is expected that a higher level of significance will be reached with the same results.

The delivery time of KB-TT plans is 8 ± 1 min, due mainly to the

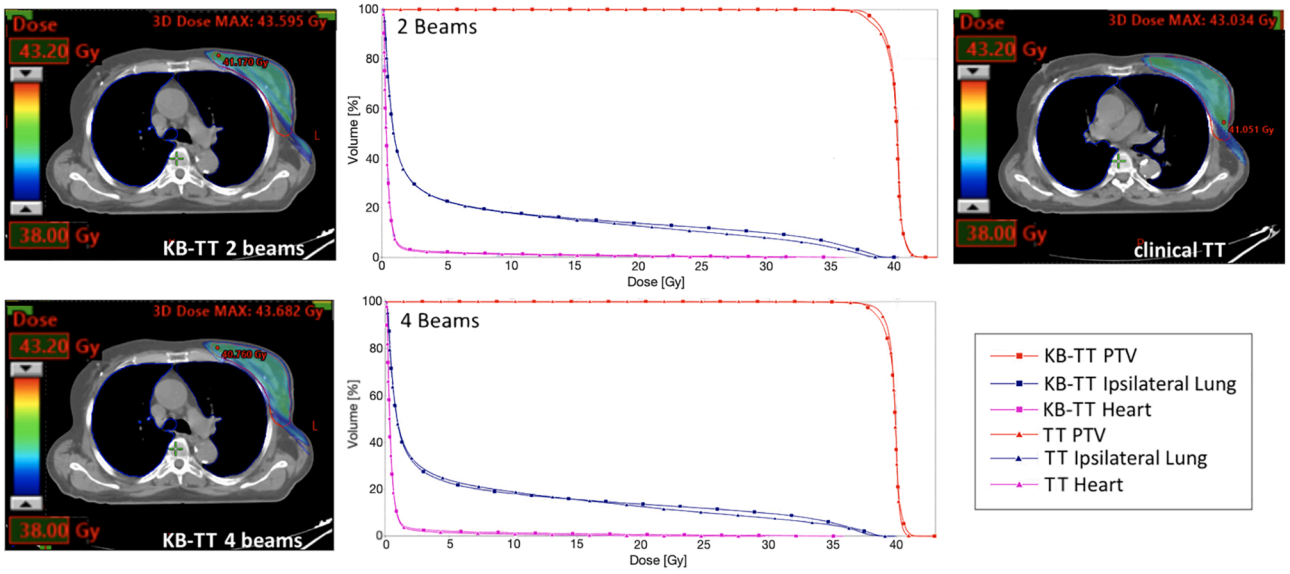

Fig. 2. Example of an unacceptable plan using two beams and modification in dose distribution adding two segments to a total of four. The color wash in the transversal CT image show the 95% of the prescription dose (38 Gy) for the two beam cases (four beam, and clinical). DVHs show the automatic plans (KB-TT) against the clinical ones (TT).

chosen field width (2.5 cm). Although 5 cm field clinical plans (65% of historical patients) are delivered in 6 ± 1 min, it was deemed necessary to use the 2.5 cm field width in order to obtain an optimal plan for the remaining 35% of patients, with the smaller field width leading to a higher modulation factor and lower pitch. In fact, smaller field width is associated with a higher conformity of the PTV dose distribution. It is expected that the use of our KB approach will reduce planning time, and importantly improve plan homogeneity between planners, avoiding sub-optimal plans. The entire process requires 25–30 min for the generation of a plan. Active planner time is from 5 to 10 min for plan template selection, ROI generation and script launching. The automatic optimization process requires approximately 20 min, but as it is a passive activity, the planner is free to work on other tasks. Preparation and optimization of a manually optimized plan would require at least 1 h. The generation of a manual WBI plans would, on the other hand, generally require significantly more time, depending on the peculiarity of the anatomy or on special requests by the clinician. The KB approach makes it possible to obtain a high quality plan from the first cycle of optimization, but if necessary, the KB-TT plan may be used as a starting point for any further refinements.

Currently, the choice of the treating beam angles is still manual and user dependent. It was decided to use the same criteria of the clinical plans for angle selection in the validation sets. This approach demonstrated that even without modifying the angles, it is possible to obtain the same or slightly better plan quality while reducing the time required to obtain it. The angle selection results in residual inter-planner variability. In principle, this process is, in principle automatable: this objective could be achieved by means of various approaches proposed in the literature; [26,38–40] the number of manual refinements would be then further reduced for this reason this could be the focus of further improvements on our approach.

The static angles modality is often preferred to helical modality or, in general, to rotational techniques as it allows the reduction of the low dose bath [13] and it is expected to be one of the most widely used techniques in centers where TT is available, due to its high performance, reported to be generally comparable or superior to the best WBI modalities [9].

The approach presented here demonstrates the possibility of replacing the manual optimization of TT planning for WBI, with KB automatic planning increasing efficiency and plan homogeneity. This approach is versatile, and the use of a commercial system is expected to facilitate a large-scale implementation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2022.06.009.

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