

**Automation in radiotherapy treatment planning: examples of use in clinical practice and future trends for a complete automated workflow**

**Automatisation de la planification du traitement par irradiation : exemples d'implémentations cliniques et futures tendances pour un flux de travail entièrement automatisé**

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## Abstract

Modern radiotherapy treatment planning is a complex and time-consuming process that requires the skills of experienced users to obtain quality plans. Since the early 2000s, the automation of this planning process has become an important research topic in radiotherapy. Today, the first commercial automated treatment planning solutions are available and implemented in a growing number of clinical radiotherapy departments. It should be noted that these various commercial solutions are based on very different methods, implying a daily practice that varies from one center to another. It is likely that this change in planning practices is still in its infancy. Indeed, the rise of artificial intelligence methods, based in particular on deep learning, has recently revived research interest in this subject. The numerous articles currently being published announce a lasting and profound transformation of radiotherapy planning practices in the years to come. From this perspective, an evolution of initial training for clinical teams and the drafting of new quality assurance recommendations is desirable.

Keywords: automated radiotherapy treatment planning - dose mimicking - dose prediction

## Résumé

La planification moderne des traitements par irradiation est un processus complexe et long qui requiert les compétences d'utilisateurs expérimentés pour obtenir des plans de qualité. Depuis le début des années 2000, l'automatisation de ce processus de planification est devenue un sujet de recherche important en radiothérapie. Aujourd'hui, les premières solutions commerciales de planification automatisée des traitements sont disponibles et mises en œuvre dans un nombre croissant de services cliniques de radiothérapie. Il faut noter que ces différentes solutions commerciales sont basées sur des méthodes très différentes, impliquant une pratique quotidienne variable d'un centre à l'autre. Il est probable que cette évolution des pratiques de planification n'en soit qu'à ses débuts. En effet, l'essor des méthodes d'intelligence artificielle, basées notamment sur le *deep learning*, a récemment relancé l'intérêt des chercheurs pour ce sujet. Les nombreux articles actuellement publiés annoncent une transformation durable et profonde des pratiques de planification des plans de traitement par irradiation dans les années à venir. Dans cette perspective, une évolution de la formation initiale des équipes cliniques et la rédaction de nouvelles recommandations d'assurance qualité sont souhaitables.

Mots-clés : planification de traitement automatisée – prédiction de dose – imitation de dose

# **Automation in radiotherapy treatment planning: examples of use in clinical practice and future trends for a complete automated workflow**

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## **1. Introduction**

Automated radiotherapy treatment planning (ATP) is slowly making its way into early clinical services. Several commercial systems based on different paradigms are now available. Current ATP techniques are often classified into three categories [1–3]: (a) automated rule implementation and reasoning (ARIR), multicriteria optimization (MCO) and knowledge-based planning (KBP). There are two approaches to MCO: *a posteriori* and *a priori* (b). Furthermore, KBP can be divided into two additional categories: (c) statistical modeling of case/atlas-based and (d) machine learning methods [4]. In the first part of this article, we present one example of the clinical implementation of commercial ATP solutions for each category (a, b, c and d) in four different French radiotherapy departments.

In parallel with this diffusion to the first clinical services, ATP remains an active area of research, notably because of the emergence of artificial intelligence (AI) [5]. In the second part of this article, we review current research, focusing only on recent ATP studies, including the final deliverable plan calculation step.

## **2. Examples of clinical implementations of commercial ATP solutions**

The following feedback illustrates the clinical implementation of commercial ATP solutions in four different French radiotherapy centers, of which a summary is given in Table 1. Note that the objective of this part is to present practical on-site implementations: the theoretical details of the ATP algorithms can be found in the literature reviews cited in the introduction.

### *2.1. Feedback on the clinical implementation of an ARIR ATP solution*

AutoPlanning (AP) in the Pinnacle (Philips Radiation Oncology Systems, Fitchburg, WI) treatment planning system (TPS) is an example of an available solution to the ARIR system. The user enters the prescription for target volumes and the constraints for organs at risk (OARs) into the optimizer. The user also defines the number of iterations per optimization. Then, the system automatically generates secondary structures allowing, among other things, the management of overlaps between the planning target volume (PTV) and OARs, the confirmation of the dose and the sparing of OARs. A cycle of five iterations corresponding to a successive creation of control structures finally leads to a solution.

In the private Amethyst radiotherapy center (Creil, France, 700 patients/y with two radiation units), Pinnacle was commissioned in 2015 with the AP module. The use of AP started while treatments using volumetric modulated arc therapy (VMAT) techniques for locations such as pelvic or head and neck tumors were increasing. Later, VMAT localizations were deployed for more complex treatments

(hippocampal sparing, breast and finally intra- and extracranial stereotactic treatments), making the use of automatic tools such as AP and scripting essential for the clinic's physicists.

Initially, AP was introduced in this hospital for the treatment of prostate cancer. The contributions of a consultant physicist and a senior physician helped to implement this system and to find an efficient and reproducible set of goals and constraints. The validation of treatment plans was performed for the first 50 cases using gamma index measurement ( $98.9\% \pm 0.7\%$ , local, 3%-3 mm) with a Delta4 Phantom (Scandidos, Sweden) and point dose measurements with a  $0.125 \text{ cm}^3$  ionization chamber (PTW, Germany) in a Plexiglas phantom ( $0.1\% \pm 0.8\%$ ).

In current practice at the radiotherapy center, ATP is performed as a combination of both AP and homemade scripts. The center employs the following workflow:

- Physicians: Perform auto-contouring based on atlas methods for main OARs, a version for corrections and validation is needed,
- Physicians: Run scripts to generate a list of empty structures (remaining OARs and target volumes) according to medical protocols (name, limits, extensions and colors) and segment manually,
- Physicists: Run scripts that load isocenters/beams/prescriptions and dose constraints in the AP module to reach protocol objectives for both the PTV and OARs. The calculation is performed during this last step.

Although the calculation time might sometimes be relatively long (up to one hour, depending on the complexity and size of the irradiated volumes), the system remains efficient in providing reliable results. Today, more than 80% of patients are treated with VMAT techniques in this radiotherapy center. Among 95% of these treatment plans (especially prostate, rectal, cervical, head and neck and lung cancers) are obtained only with AP, without additional manual optimization. The team experience allowed to continuously improve the constraints in the templates and generate the final treatment plans more quickly. This methodology not only allowed to progressively implement new techniques with an accelerated learning curve but also to reduce interoperator variability.

## *2.2. Feedback on a clinical implementation of an atlas-based KBP solution*

Rapidplan (Varian Medical Systems, Palo Alto, CA) is an atlas-based KBP solution that provides estimated dose-volume histograms (DVH) on the basis of patient contours, beam setup, dose prescription and an associated estimation model. The estimated DVHs are used to generate automatic objectives for inverse planning optimization. The software uses principal component analysis to extract the correlations between dosimetric and geometric features in a training data set for each OAR of the model. This results in an OAR regression model and the ability to predict DVH for each new patient. The estimation model can be built on a database of treatment plans from the center or provided by the manufacturer.

Institut du Cancer – Avignon Provence (Avignon, France, 2800 patients/y with six radiation units) is a public cancer center in which Rapidplan was implemented in 2015. Dedicated models were built to reflect the current practice in the center. Two models were developed: one for VMAT prostate/seminal vesicle treatments with one single prescription (80 Gy / 54 Gy / 40 fractions) and three OARs and a broad scope head and neck VMAT model, with clinical sites from the larynx to nasopharynx, corresponding to different dose prescriptions and 16 OARs.

Training datasets were composed of 100-150 carefully selected plans with well-defined trade-offs and consistent OAR contours. Model validation is a two-step process: first, the DVH estimation part is evaluated, and outliers are processed (i.e., plans different from the rest of the database, which biased the regression model). Second, the optimization criteria extracted from the estimation are fine-tuned to match the user expectations (priorities, supplementary hard constraints).

Models were evaluated on 20 new patients not included in the database. Homogeneity, efficiency and quality were improved with Rapidplan compared to manual optimization. Eighty-three percent of the plans met the clinical criteria in a single optimization. The only failures came from plans whose geometry was different from those in the database (e.g., larger OAR or PTV-OAR overlap). This suggested increasing the variability of the plans in the database to help the model provide an optimal solution for various geometries. The DVH estimation added only a few minutes compared to a standard plan generation.

The greatest strength of Rapidplan is DVH estimation. Its ability to generate the DVH of an optimal plan can be used to assess the quality of plans in a clinical trial [6]. The greatest weakness is the tuning of the objectives. Finding the desired tradeoffs for the final plans can be time consuming. One limitation is that the model can only provide the best of what it has learned. Maintenance is needed to reflect improvements in treatment techniques and for version upgrades. However, the models show good versatility with the ability to be easily tweaked to work with different prescriptions or different treatment machines (single stack multileaf collimator of a TrueBeam versus double stack of a Halcyon). An evaluation is currently being performed in the center to use Rapidplan combined with a posteriori MCO. The development of models for other treatment sites, such as the cervix, breast and lung, is also planned.

### *2.3. Feedback on a clinical implementation of a machine learning (ML)-based KBP solution*

RayStation v9B autoplanning (Raysearch Laboratories, Sweden) is a ML-based KBP solution. It uses a random forest model trained with a database of treatment plans (CT, dose map and ROIs) coming from Raysearch Laboratories (RS model) or from the clinic (local model). For a new patient, the ML process assigns a dose value for each voxel. Then, the new dose map is sent to the “mimicker”, which transforms the ML dose distribution to an objective function for the optimization module to make it deliverable. A given model (RS or local) can be locally adapted for two close locations or for different prescriptions (for example, a 78 Gy prostate and a 66 Gy prostate bed prescription).

In the Oncorad Garonne Group private radiotherapy center (Toulouse, France, 2500 patients/y with seven radiation units). VMAT planning is performed with RayStation v9B. The group had its first ML model (RS) in July 2020. Since then, it has optimized its own ML models (local model) for pelvic treatment plans obtained from 50 plans with lymph nodes and 100 plans without nodes to treat the male pelvis at 78 Gy for the prostate (with seminal vesicles and lymphatics nodes) irradiation and 66 Gy for the prostate bed (with lymphatics nodes).

The ML plans were evaluated qualitatively (visualization) and quantitatively with clinical goals, a homogeneity index, a conformity index and a dose gradient index [7]. Eighty percent of the automatic plans were acceptable without new optimizations and were generated in approximately 16 minutes.

ML integration in the clinical routine is performed with Python scripts to standardize the planning and to decrease planning time. To prevent errors due to scripting, some key control points were kept

during the automatic process: validation was required after each main step. Physicists and a PhD student were trained by Raysearch for TPS python scripting. For ML, one physicist and the PhD student were directly involved in developing and adapting ML local models. Dosimetrists were trained by physicists for the use of scripts.

The main difficulty in obtaining an ML local model lies in the patient's database construction, which is time-consuming (it requires 50 to 100 homogenized plans). The most challenging part of the planning workflow is the adaptation of the ML model to suit all patients and all prescriptions.

The dose measurements for TPS commissioning were performed with a 3DS water tank (SunNuclear, USA) and microdiamond detector (PTW, Germany). Matching between measurements and ML calculations followed IAEA 1583/1540 and SFPM 27 report recommendations. VMAT patient QA was performed with an ARCHECK 3D matrix and EPID Dosimetry with SunCheck (SunNuclear, USA). The patient QA results were the same with or without ML, i.e., more than 95% points with a gamma index  $<1$  for 3%-2 mm (local).

#### *2.4. Feedback on a preclinical implementation of an a priori MCO solution*

The autoplanning solution (mCycle) proposed by Elekta Company (Elekta AB, Sweden) uses an *a priori*-MCO plan optimization algorithm that was first developed and implemented in the Erasmus MC Cancer Center Institute. At that time, the Erasmus-iCycle algorithm needed to be converted to Monaco plans to generate clinical plans. It has now been implemented in a research version of the Monaco TPS (Elekta AB, Sweden, v 5.59.11), which is currently not commercially available. The solution was evaluated for 18 months at Leon Berard Comprehensive Cancer Center (Lyon, France 3500 patients/y with eight radiation units) as part of a research partnership with Elekta.

The algorithm directly and automatically generates a single Pareto-optimal plan for each new patient using a “wish-list” with predefined clinical dose objectives or constraints on OARs and PTVs based on a protocol. The optimization stage has two passes. During the first pass, mCycle optimizes the individual objectives to meet the different requested goal values while respecting the priority order and all defined constraints. If the goal value cannot be achieved, it is constrained at the achieved value and excluded from the second pass for further dose reduction. If the achieved value is below the goal dose, the goal dose is constrained, leaving optimization space for the lower prioritized objectives. During the second pass, the optimizer further reduces the doses that are below the goal value in the first pass as low as possible. One major advantage of mCycle is that it does not stop optimization at the set objective goals but always minimizes the dose to OARs and unspecified tissues.

To obtain a robust wish list, each protocol is discussed with the clinical team to assign the plan constraints and priority for each OAR objective. The first aim is to mimic the clinical plans. This can be achieved using existing optimization templates, sequencing parameters from the clinical version of the Monaco TPS and modifying some cost functions to take advantage of the new optimization algorithms. An evaluation of the current wish list is made after applying it to a restricted number of patients (typically 4-5) per protocol. The wish list is then updated until an optimal solution is obtained for all cases. At this step, the goal is to improve the clinical plans. The process is stopped when it is considered that further improvements are impossible. Then, it is applied to a larger cohort (10 patients) and validated if no failure is observed. Hence, it might take time to generate a robust wish list if many OARs have to be considered (i.e., Head-and-neck cancer), but once validated for one clinical protocol and for localization, it can be quickly adapted to another dose protocol.

Since the solution is available at Leon Berard Cancer Center, wish lists for prostate cancer (60 Gy/20 fr), breast cancer and head-and-neck cancer (70 Gy-54 Gy/35 fr) have been elaborated. Once the wish lists are established, the optimization time is 50-60 min for a head-and-neck case and less for prostate or breast cases (30-45 min). The performances of mCycle versus manual plans were assessed on a cohort of 28 head-and-neck cases (including nasopharyngeal carcinoma). All plans were considered clinically acceptable by the physicians without any manual adjustment of the wish list. Notably, mCycle plans were considered better than manual plans in 75% of cases. The number of MUs (+30%) and the complexity of the plan were significantly increased with mCycle compared to manual plans, but QA results were not impacted (minimum gamma pass rate of 95.7% using the ArcCheck device; analysis criteria: 3%-3 mm, global analysis method). Conversely, the delivery time was increased by 20% with mCycle

### **3. Minireview of complete ATP pipeline research articles**

While the first ATP solutions are being implemented in clinical departments, research in this area continues to intensify, particularly due to the democratization of deep learning methods. Most papers deal with dose map prediction, starting from planning CT images and contoured structures. A proof of the strength and interest in this research topic was an open-access dose prediction grand challenge that recently gathered 195 participants from 28 countries [8]. However, a good prediction model does not guarantee obtaining a good deliverable plan in an ATP workflow [9].

This is why an increasing number of research teams are interested in the complete ATP pipeline, including the creation of deliverable treatment plans: these papers (published after 2020) are the focus of this mini-review. Table 2 summarizes articles published from 2020 to April 2021 that address obtaining deliverable plans in an ATP process. For articles published before 2020, we recommend Netherthron and Wang's literature reviews on IA for ATP [2,5].

Two main models are conventionally used to convert dose distributions to deliverable plans: dose mimicking and inverse optimization [3,9]. Dose mimicking consists of automatically minimizing the differences between a dose distribution prediction input and the deliverable dose output, while the inverse optimization method basically consists of using predicted optimization weights/constraints in a conventional optimization model. The inputs for these models can be IMRT objective sets [10], 3D dose distributions [11–13] and, more recently, probability distributions of dose [14,15]. This latest type of input may help to better manage specific dosimetric and clinical trade-off problems in the ATP workflow.

However, other methods have been recently developed to obtain deliverable plans, such as predicting fluence maps. Fluence maps are predicted either via a dose distribution prediction step [16,17] or even directly from planning images and contoured structures [18,19]. The advantage of this method is that there is no need for an inverse planning step, and fluence maps are easily processed by commercial TPSs to generate deliverable plans.

Finally, a new method based on reinforcement learning (RL) has been investigated in the ATP process. This method has been successfully used in complex decision-making problems such as video or Go games. It has the advantage of not requiring a predictive model by gradually integrating human experience. In an ATP approach, RL has recently been used for direct tuning of optimization weights [20] or machine parameters [21].

Concerning the prediction step, the methods used in the different articles we reviewed are varied (see Table 2): random forest, Bayesian networks, CNN, GAN, U-Net... These methods are based on

the use of contoured structures with or without the planning CT, keeping the integrity of the information or using different means of dimensionality reduction. As stated above, the predictions output range from an IMRT objectives set to fluence maps. Depending on the studies, mimicking, inverse optimization or fluence map processing is performed with commercial or in-house TPS.

#### **4. Conclusion**

In this work, we have presented different clinical implementations of current commercial ATP methods, showing the diversity of possible practices. ATP practice may nevertheless still evolve strongly in the coming decade, as we have pointed out in a mini-review of research papers dedicated to full AI-based ATP pipelines. From this perspective, it becomes essential that clinical teams be properly prepared through an evolution of initial training [22] and dedicated quality assurance recommendations [23].



**Table 1**

Summary of feedback from four teams that have clinically implemented different automated treatment planning solutions. Note that the elements presented in this table reflect the subjective experience of each team and are not intended to allow an objective comparison between the four ATP solutions.

	Center 1	Center 2	Center 3	Center 4*
<b>TPS/Module</b>	Pinnacle AutoPlanning (Philips Radiation Oncology Systems, USA)	Eclipse Rapidplan (Varian Medical Systems, USA)	RayStation auto planning (Raysearch Laboratories, Sweden)	mCycle (Elekta AB, Sweden)
<b>Version</b>	P16.2	15.6	9B	Research version
<b>Method</b>	Automated rule implementation and reasoning	Atlas-based knowledge-based planning solution	Machine learning knowledge-based planning solution	<i>A-priori</i> multicriteria optimization
<b>Date of clinical set-up</b>	2015	2015	2020	NA
<b>Initially treated localizations</b>	Prostate	Prostate	Prostate	Prostate, breast and H&N (not clinically treated)
<b>Currently treated localizations</b>	Prostate, rectum, cervix, H&N, lung	Prostate and H&N	Prostate	NA
<b>Initial commissioning</b>	Validation on 50 cases with Delta4 and ionization chamber measurements	Validation on 20 cases with EPID and Delta4	NK	Validation performed on 28 head-and-neck cases with ArcCheck measurements

<b>Number of patients treated with AutoPlanning to date</b>	>2000	>2000	NK	NA
<b>Training database mandatory?</b>	No	Yes	Yes (~100 + 10 validation patients)	No
<b>Classical optimization?</b>	Yes	Yes	No (no need of objectives templates)	Needs objectives templates
<b>Adjustable settings intra/inter localizations</b>	Dose Fall-Off	All optimization parameters can be adjusted (priorities, constraints, volumes)	Adjustable to prescription and localization modifications, if targets and OARs are not too different	Dose objectives/constraints to targets/OARs
	Priority Target/OAR			Priority order of the objectives
	Maximum dose thresholds (%)			Sufficient values (when the goal is achieved)
<b>Calculation time</b>	Extended Pelvis, 3 mm Grid, 2 Full Arcs: approximately 1 h Stereotactic brain, 2.5 mm Grid, 4 Partial Arcs: approximately 25 min	2 minutes in addition to a classical plan generation (20 min H&N 4Full arcs 2.5 mm grid)	15-20 min. Faster if less iterations.  Voxel 2.5 mm	30-55 min Voxel 3 mm
<b>Advantages</b>	Fast inverse planning learning curve	Fast	Fast	Single optimal solution
	Fast clinical use upon installation	Improves plan homogeneity	Several strategies can be automated to take into account	No manual adjustment/no learning curve

			the most common scenarios	
	Easy to use and clinical approach	Improves plan quality	Requires only one verification	No training database needed
	No training database needed	Statistical tools included to evaluate the quality of the models	Improves plan homogeneity	Quick adaptation of the wish list for a single localization but different protocol
	Adaptation possible for stereotactic treatments	Provides an optimized base plan for a-posteriori MCO	Plans can come from several experts at the same time	no interoperator variability once robust wish list is established
	Manual adjustment possible	Possibility to adapt to a different dose prescription or machine		
<b>Drawbacks</b>	Association with Scripts for daily optimization	Database of 100-150 quality plans required	Requires a database of 100 plans before making the model. Plan quality must be the best possible.	Time for elaborating a robust wish list (head-and-neck)
	Calculation time			Calculation time
	Difficult to act on some dosimetric choices (preferred irradiation zones, distribution of medium and low doses, etc.)			Wish list is operator-dependent- to be expert in Monaco planning is a plus: need for providing reference wish lists as starting points for new users

H&N: head and neck; NA : non applicable; NK : not known

\*preclinical version, some items are NA

**Table 2**

Studies on automated radiotherapy treatment planning, including the creation of deliverable plans, that were published between January 2020 and April 2021.

Reference		Prediction step		Prediction output = input for obtaining deliverable plan	Obtaining deliverable plans step		Major Contribution/ Highlights
		Patient cohort*	Input data**		Method	Dose calculation	
[12]	105 IMRT breast plans	CS + CT	Two models: U- net and atlas regression forest	3D dose distribution	Dose mimicking	Raystation TPS	The first study focusing on dose prediction for breast cancer, with the use of CNNs
[14]	94 VMAT prostate plans	Five CS	U-net	Probability distribution of dose		Raystation TPS	Probabilistic model, including the uncertainty of predictive distributions.
[15]	94 VMAT prostate plans	Seven CS	Variational autoencoder + Bayesian	Probability distribution of dose		Raystation TPS	Probabilistic model, including the uncertainty of predictive distributions. Use of dimensionality reduction to preprocess prediction input data.
[10]	140 IMRT	Seven CS	CNN	IMRT objectives set	Inverse	Pinnacle TPS	CNN model implemented to perform a

	cervical plans				optimization		prediction of patient specific IMRT objectives settings in Pinnacle
[11]	217 IMRT H&N plans	11 CS + CT	GAN	3D dose distribution***		In-house	Full 3D-dose predictions using a generative adversarial network and scaling of dose predictions pre-fluence map optimization.
[13]	81 VMAT H&N plans	CS	Two models: FBP and U-net	3D dose distribution***		Eclipse TPS	FBP method: no need for training data
[16]	100 IMRT SBRT pancreatic plans	CS + CT	CNN (3D dose distribution) + U-Net	Fluence map	NA	Eclipse TPS	A double CNN framework capable of directly predicting a fluence map from contour and CT alone
[17]	102 VMAT H&N and 14 prostate plans	3D dose distribution	U-Net	Fluence map		In-house	Fluence map prediction from dose distribution in phantom geometry and scaling to patient geometry
[18]	231 IMRT H&N plans	11 CS + CT	GAN	Fluence map		Eclipse TPS	Direct prediction of the fluence map from 2D structures projections
[19]	120 IMRT prostate plans	Six CS + CT	Dense residual hybrid network	Fluence map		Eclipse TPS	Direct prediction of the fluence map from 2D structures projections

[20]	74 IMRT prostate plans (10 for training)	Intelligent planning behaviors autonomously generated through a deep reinforcement learning process	Direct tuning of optimization weights via reinforcement learning
[21]	40 VMAT/IMRT prostate plans (15 for training)		Direct control of machine parameters via reinforcement learning

CS: contoured structures; H&N: head and neck; IMRT: intensity modulated radiotherapy; VMAT: volumetric modulated arc therapy; SBRT: stereotactic body radiotherapy; GAN: generative adversarial network; CNN: convolutional neural network; FBP: filtered back projection; TPS: treatment planning system; CT: computed tomography

\* without distinction between those used for training, validation and tests

\*\* number of structures given if available

\*\*\* IMRT objectives set are then estimated from the 3D dose distribution

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