



## Review Article

# From pre-clinical studies to human treatment with proton-minibeam radiation therapy: adapted Idea, Development, Exploration, Assessment and Long-term evaluation (IDEAL) framework for innovation in radiotherapy

Emmanuel Jouglar<sup>a,b,\*</sup>, Ludovic de Marzi<sup>a,c</sup>, Pierre Verrelle<sup>d</sup>, Gilles Créhange<sup>a,c</sup>, Regis Ferrand<sup>a</sup>, François Doz<sup>e</sup>, Yolanda Prezado<sup>b</sup>, Xavier Paoletti<sup>f</sup>

<sup>a</sup> Institut Curie, PSL Research University, Department of Radiation Oncology - Paris and Orsay Protontherapy Center, Paris, France

<sup>b</sup> Paris-Saclay University, CNRS UMR3347, Inserm U1021, Signalisation Radiobiologie et Cancer, Orsay, France

<sup>c</sup> Institut Curie, PSL Research University, Inserm U1288, Laboratoire d'Imagerie Translationnelle en Oncologie (LITO), Orsay, France

<sup>d</sup> Institut Curie, PSL Research University, CNRS UMR9187, Inserm U1196, Orsay, France

<sup>e</sup> SIREDO Centre (Care, Innovation and Research in Pediatric, Adolescent and Young Adults Oncology), Institut Curie, Paris and University Paris Cité, Paris, France

<sup>f</sup> Institut Curie, PSL Research University, Biostatistic Unit, Paris, France



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## ABSTRACT

The implementation and spread of new radiation therapy (RT) techniques are often rushed through before or without high-quality proof of a clinical benefit. The framework for phase 1, 2 and 3 trials, ideally designed for pharmaceutical evaluation, is not always appropriate for RT interventions. The IDEAL framework is a five-step process initially developed to enable the rapid implementation of surgical innovations while limiting risks for patients. IDEAL was subsequently adapted to RT. Proton-minibeam radiation therapy (pMBRT) is an innovative RT approach, using an array of parallel thin beams resulting in an outstanding increase in the therapeutic ratio. Cumulative preclinical evidence showed pMBRT was superior to standard RT regarding brain tolerance and provided equivalent or better local control in several glioblastoma models. We decided to adapt IDEAL to pMBRT to accelerate the implementation of this promising new technique in clinical care and present here some examples of possible upcoming studies

## Introduction

Innovation in medicine, particularly in radiotherapy (RT) is rapidly evolving alongside technological advancements. Improvements in technology occur very fast while trials to evaluate medical interventions take much longer. Yet, as physicians want to offer the best available treatment to their patients, several new RT techniques have been implemented before high-level evidence of their advantages has been published, e.g. intensity modulated radiation therapy (IMRT) in head and neck cancer or proton therapy (PT) for children [1,2]. Standard clinical trial phases (1–3) are more suited for drug testing than for evaluating new RT. This is especially true when introducing a new technique. Idea, Development, Exploration, Assessment and Long-term evaluation (IDEAL) is a systematic five-step process that was originally developed for surgical innovation, and has been adapted to RT for MR-

Linac [3–5]. This process aims to facilitate safe and timely access to the new technique without implementing unrealistic rules that would hinder innovation.

One primary goal of RT innovation is to widen the therapeutic ratio by increasing efficacy and/or improving tolerance. Primary and secondary brain tumors are associated with high morbidity and mortality and particularly require improved therapies. On the one hand, high-grade gliomas, including glioblastoma, are one of the most frequent primitive brain tumors in children and adults. Current treatment results in close-to-100 % recurrence rate [6]. On the other hand, brain metastases (BM) develop in 10 to 30 % of adult patients with solid tumors [7]. Among the therapeutic arsenal, photon stereotactic RT with few high-dose fractions may be indicated for the first-line treatment (BM) or in reirradiation (BM or glioblastoma) [8,9]. Although treatment of small lesions ( $\leq 2$  cm) results in good local control and tolerance, the

\* Corresponding author at: Institut Curie, PSL Research University, Department of Radiation Oncology - Paris and Orsay Protontherapy Center, Paris, France.

E-mail address: [emmanuel.jouglar@curie.fr](mailto:emmanuel.jouglar@curie.fr) (E. Jouglar).

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treatment of large tumors is still challenging: the high risk of neurologic toxicity, especially in the case of reirradiation, leads to a reduction in the prescribed dose and drastically reduces local control [10]. In children and adolescents-young adults (AYA), reirradiation for gliomas may be discussed. The second RT is generally delivered with a normofractionated regimen, and primarily aims to decrease briefly tumor symptoms, as median progression-free survival (PFS) after reirradiation remains a few months [11–13]. In these diseases, dose escalation would be needed to improve outcomes, but treatment with current technologies would translate into unacceptable side-effects, such as radiation necrosis [10,14].

As a recently developed technology with high potential for improving patient outcomes, proton-minibeam radiation therapy (pMBRT) is considered an innovation in RT [15]. This new technique of spatially fractionated RT (SFRT) modulates the dose to create alternating regions of high and low doses, in contrast to the homogeneous dose distributions used in standard RT (Fig. 1). MBRT with protons (and other heavy ions) offers several advantages: a negligible dose is delivered to normal tissues beyond the Bragg peak; the sharp lateral penumbra allows a dose distribution highly conformal to the target volume; the dose distribution can be easily modulated either with a homogenous dose in the tumor while keeping protective peak-and-valley-dose profile in normal tissues or by keeping an inhomogeneous dose which has been associated with a better tumor control in some preclinical studies (Fig. 1) [16]. Indeed, pMBRT seems to activate different biological mechanisms from those involved with direct damage by ionizing radiation [17]. In preclinical brain models, pMBRT as compared with standard PT has demonstrated significantly reduced toxicity [18,19]. Reduced skin toxicity has also been demonstrated by other teams [20]. pMBRT has shown anti-tumoral effect equal or superior to standard PT without major side effects observed in the latter in different rat glioma models, thus opening the possibility of more aggressive irradiation schemes [16,19,21–23]. Indeed, 70 % long-term survival (> 6 months, free of tumor) could be obtained with pMBRT without significant normal tissue damage. Although the underlying biological mechanisms in MBRT are not completely understood, we have gathered evidence indicating that the immune system plays a determinant role in the antitumor response [24]. Initial studies suggest that pMBRT could provoke long-term antitumor memory, potentially reducing recurrence rates in resistant tumors. pMBRT plans for human treatments were then compared with standard PT plans and met the criteria recommended for clinically acceptable dose-volume histograms in organs at risk [25]. We also showed that pMBRT led to a significant decrease in the dose to the organs at risk compared to stereotactic photon RT for the treatment of metastasis [26]. However, the clinical implementation of pMBRT presents a number of challenges. First, from a technological point of view,

the use of minibeam presents difficulties in terms of experimental methods and dosimetric characterisation. Work is underway, for example, to develop new primary standard dosimetry protocols for such small beams [27]. Second, new methods for optimizing, prescribing, and reporting doses still need to be developed, in particular using clinical tools. For example, procedures for evaluating treatment plans need to be standardized, the spatial resolution of calculations improved, and possible radiobiological models compared with (pre)clinical data [28].

Other SFRT techniques using larger beams have already been used in clinical practice (such as GRID and Lattice therapy) [28–31]. Recently, Grams and colleagues published the first use of MBRT on patients using a clinical orthovoltage unit [32]. However, MBRT with proton or other heavy particles has yet never been used on patients.

This article outlines the step-by-step implementation of pMBRT at Institut Curie for treating brain tumors in both adults and children, guided by the IDEAL framework.

### The Idea, Development, Exploration, assessment and long-term evaluation process

The IDEAL stages and their key features for assessing innovations in RT such as pMBRT are summarized in Table 1.

#### Stage 0: radiotherapy predicate studies

Stage 0 gathers all of the preparatory work necessary for the use of the innovation in human patients. It aims to answer questions about how and in whom the innovation should be used. This includes preclinical studies that evaluate the safety and efficacy of pMBRT. Strong preclinical data have already shown that pMBRT results in less toxicity compared to standard treatments while providing similar or even stronger anti-tumor effects [16,18,19,21–23]. This stage involves carefully selecting the dose and parameters for radiation delivery, as techniques like SFRT require attention to factors like the mean, minimum and maximum doses, the peak-to-valley dose ratio (PVDR), beam width and spacing, which all influence biological response. Specific beam parameters such as the energy, dose rate or geometrical/dose uncertainties related to the irradiation technique (collimation, respiratory motion etc.) also play a role. Furthermore, stage 0 includes evaluating the conformity of the treatment planning system, record and verify system, beam delivery and patient quality control. Best clinical practice recommendations on technical aspects can be found in ICRU reports, whereas guidance for physics in clinical trials are described in other recent reports [33–35]. Radioprotection issues for patients and staff is also to be addressed [36]. In-silico planning studies to compare with standard treatment may help to estimate clinical benefit and in the

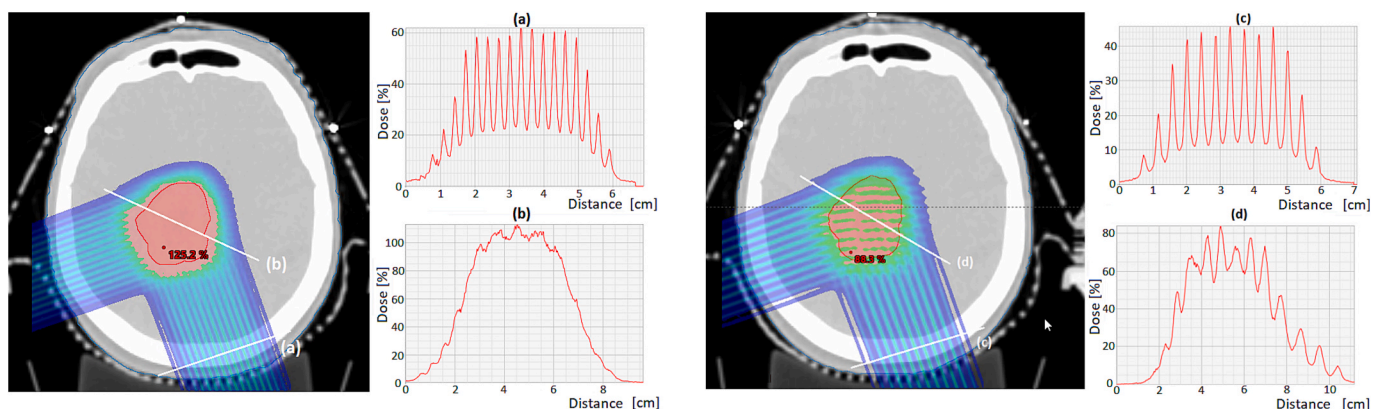


Fig. 1. Dose distributions of proton-minibeam radiation therapy for a glioma case and two different centre-to-centre (ctc) configurations. Dose profiles plotted in the healthy tissue region and in the target volume for a ctc of 3 mm (a and b) and 4 mm (c and d). From pre-clinical studies to human treatment with proton-minibeam radiation therapy: adapted IDEAL framework for innovation in radiotherapy.

**Table 1**  
IDEAL stages for innovations in radiation oncology – proton-minibeam radiotherapy.

	Stage 0	Idea Stage 1	Development Stage 2a	Exploration Stage 2b	Assessment Stage 3	Long-term evaluation Stage 4
Purpose	- Preliminary work - How and in whom to use the innovation?	First time use of the innovation in patient	Technical optimization of the innovation for treatment delivery	Provide proof of early clinical effectiveness and safety of the innovation	Formal comparison of innovation against standard treatment	Long-term outcomes of the innovation, post-marketing and surveillance
Outcomes	- Patient selection - RT parameters - Uncertainties and evaluation of conformity - Radioprotection control	- Proof of concept - Early toxicity	- Feasibility and safety - Technical improvements	- Toxicity - Early effectiveness - Tumor response - Local recurrence (with spatial information)	- Effectiveness compared to standard treatment: oncologic outcomes (progression free survival, overall survival, pattern of recurrence...) - Toxicity, including patient reported outcomes - Cost-effectiveness	- Long-term toxicity - Long-term (disease free) survival - Rare side effects - Patient reported outcomes
Study types or design	- Preclinical study - In-silico planning study - Early health technology assessment study	Structured case report on one or few patients	Prospective small uninterrupted case series	Prospective study with preferably randomized component: randomized control trial, random allocation of limited available treatment slots to eligible patients, comparison with matched (historical) controls	RCT	Prospective registry, including all patients treated with the innovation
- Example 1 - Brain tumors in adults	In-silico planning study comparing pMBRT and standard treatment in patients with brain tumors	Report of the first use of pMBRT in an adult patient with recurrent glioblastoma eligible for re-irradiation	Small prospective cohort study with dose escalation for the treatment of recurrent glioblastoma eligible for re-irradiation in adults	Prospective expansion cohorts of adult patients with recurrent glioblastoma eligible for re-irradiation or with large brain metastases (basket trial) treated by pMBRT with the dose defined in a previous dose-escalation study	(Multicenter) RCT comparing standard radio-chemotherapy versus standard radio-chemotherapy + pMBRT boost for first-line treatment of glioblastoma in adults with initial safety study	Registry collecting patient and tumor characteristics, imaging, treatment data, toxicity and survival outcomes of all patients treated with pMBRT
Example 2 - Brain tumors in children and AYA			Small prospective cohort study with dose escalation for the treatment of recurrent high-grade glioma eligible for re-irradiation in children and AYA	Prospective expansion cohort of pediatric and AYA patients with recurrent high-grade glioma eligible for re-irradiation treated by pMBRT	(Multicenter) RCT comparing standard irradiation to standard irradiation + boost with pMBRT for first-line treatment for high-grade glioma in children and AYA	

Abbreviations: RT, radiotherapy; RCT, randomized control trial; AYA, adolescents and young adults; PFS, progression-free survival

selection of patients [37]. Early health technology assessments may be used to evaluate the cost-effectiveness of the innovation [38].

Here, brain tumors were selected as appropriate clinical cases for pMBRT due to the need for improvements in prognosis and tolerance of treatment and the large preclinical evidence supporting the potential of pMBRT for improving both tumor control and organ tolerance. One Stage-0 study example that aims to determine the adequate tumor and patient candidates for pMBRT is an in-silico planning study comparing standard irradiation to pMBRT in patients with recurrent glioblastoma and large brain metastases (>2-cm diameter), with or without prior irradiation. All patients are to be previously treated at our institution with stereotactic RT. The pMBRT plans will be compared to stereotactic photon and proton therapy in terms of target coverage and dose to organs at risk, in order to determine the optimal parameters of pMBRT for use in the next steps. In parallel, we will evaluate in-silico the possibility of a dose-escalation using pMBRT in these patients. The Figure shows a pMBRT example of treatment plan and dose distributions for a glioma case, computed using Varian ECLIPSE software (version 15.6.03) and TOPAS Monte Carlo simulations. Two pMBRT configurations are considered, obtained using a 65 mm thick multislit brass collimator placed between the nozzle and the patient: a narrow centre-to-centre (ctc) distance of 3 mm, providing a uniform dose distribution in the PTV, and a larger ctc distance of 4 mm with increased spatial

fractionation in normal tissues (at the cost of PTV homogeneity). The width of the slits used to shape the minibeam was 400 µm at the collimator location. The PVDR of dose profiles in normal tissues were 2.8 and 3.8 for the ctc of 3 mm and 4 mm, respectively, with valley doses representing 20 % of the prescribed dose to the PTV (at the profile location). The PVDR evaluated in the PTV region were 1.06 and 1.3 for the ctc of 3 mm and 4 mm, respectively.

#### Stage 1: idea

In Stage 1, the innovation is used for the first time. Reports will demonstrate the feasibility and absence of unexpected toxicity of the innovation in a few highly-selected patients.

A key example will be the first clinical use of pMBRT in a patient with recurrent glioblastoma, which will be documented as a case report. This report will detail the treatment process, technical aspects, and early tolerance, with the patient enrolled in a prospective phase 1 clinical trial as described in Stage 2a. The main inclusion criteria will lead to the enrollment of patients usually considered for high-dose reirradiation, such as: local recurrence after any line of treatment, including first-line RT, documented by MRI with a single lesion of size ≤ 4.0 cm on T1 post-gadolinium sequence; the recurrence is confirmed, and focal reirradiation decided upon in multidisciplinary tumor board; the reirradiation

target volume is at least partly encompassed by previous prescription isodose; and prior first line RT must have ended at least 12 weeks before the reirradiation treatment.

#### Stage 2a: development

Stage 2a aims to demonstrate the feasibility and safety of the innovation in a small group of 10 to 30 patients. It allows for technical adjustments and refinements. Stages 1 and 2a may be merged and take the form of a prospective trial with ethical approval. Predetermined rules for stopping the trial and monitoring safety are advised. The report will show inclusion criteria, describe the procedure and any technical modifications made and report toxicity.

For instance, pMBRT will be tested in a dose-escalation study with adult patients with recurrent glioblastoma (see Stage 1 for inclusion criteria), and secondly in children/AYA with recurrent high-grade glioma. Data will be analyzed according to the time-to-event continual reassessment method, which is particularly suitable for evaluating the late toxicity of RT without excessively expanding the overall duration of the trial [39]. The primary objective would be to identify the maximum tolerated dose (MTD) based on the occurrence of dose-limiting toxicities (DLT) and the recommended dose. Special attention will be given to toxicity related to the central nervous system, especially radio-necrosis. Whereas the MTD can be defined on a short DLT evaluation period (few months), the recommended dose should incorporate the evaluation of DLT over the complete follow-up of the patients, raising the question of possible competing events that need to be addressed [40]. Parallel expansion cohorts in several indications provide a powerful tool to broaden toxicity evaluation.

#### Stage 2b: exploration

In Stage 2b, the innovation evaluation goes from technical refinement to the clinical evaluation of effectiveness. Outcomes in this stage are toxicity and early efficacy (tumor response, local control, PFS, overall survival). In cases with early recurrence, the pattern of failure is described (e.g., in-field recurrence may suggest underdosing, marginal failure may imply margin shortfall). Prospective study in a basket-type design, possibly with a comparative component, such as randomized control trials (RCT) may be used to compare with conventional RT. The expected benefit of a single protocol with multiple indications is to strengthen pooled analyses, while adapting the cohorts to emerging evidence from the translational research program [41]. In case of limited access to the innovation, random allocation of slots to eligible patients can be considered. If randomization is difficult to carry out due to lack of adequate standard or paucity of the population, cohort studies and prospective registries with matched (historical or contemporary) controls may be quality alternatives.

For example, Stage 2b for pMBRT might involve prospective expansion cohorts of adult patients with brain tumors, including patients with large brain metastases or recurrence of glioblastoma with indication of focal (re)irradiation and will be treated with pMBRT with the dose defined in the previous stage. The primary objective would be assessing the 6-month local control rate with rates above 85 % for brain metastasis and 50 % and recurrent glioblastoma considered promising. On the other hand, an expansion cohort of pediatric/AYA patients with high-grade glioma eligible for re-irradiation could also be included with PFS as the primary endpoint. If early signs of efficacy are observed, randomization between dose-escalated pMBRT and standard RT may follow. This adaptive design balances the methodological requirement of a control to propose a promising treatment to patients with terrible prognosis.

#### Stage 3: assessment

Stage 3 aims to compare the innovation against standard therapy.

This stage typically involves larger cohorts (more than 100 patients). The preferred study design is RCT. RT quality control is recommended and may include procedures for site activation (facility questionnaire and beam output audit, dummy run), prospective or retrospective case review (delineation and RT plan) [42].

An example of a Stage 3 study with pMBRT is a (multicenter) RCT comparing mid- and long-term survival, toxicity, quality of life, and cost-effectiveness of standard treatment (surgical resection followed by radio-chemotherapy) with or without a pMBRT boost for first-line treatment of glioblastoma in adults. The parallel study in children/AYA could also test the addition of pMBRT to the first-line treatment of high-grade glioma. The primary objective would be 6-month PFS. The studies will begin with a short safety study to verify tolerance of adding a pMBRT boost.

#### Stage 4: long-term study

The objective of Stage 4 is to look at long-term outcomes of the new technique and to detect rare side effects. This stage involves establishing a prospective registry that collects all relevant data. Datamining approaches and models can be used to explore tumor control probability, and explore relationships between radiotherapy parameters and outcomes [43–45].

The Institut Curie has planned to create a dedicated database to prospectively track all patients treated with pMBRT, facilitating long-term follow-up and research. This registry will gather patient and tumor characteristics, imaging, treatment data (including MBRT parameters), toxicity and survival outcomes.

## Discussion

Obtaining high-quality evidence of the benefits of innovation in RT is challenging. Here, we present the Institut Curie's 5-step process for implementing an innovative spatially fractionated radiation technique, pMBRT. The Institut Curie research team has gathered a large amount of pre-clinical data showing the potential advantages of pMBRT in enhancing the therapeutic ratio [16,19,22,24]. The first step involves evaluating pMBRT in poor-prognosis diseases with a well-known RT dose–effect relationship, but no possibility of dose escalation with current technology. Such situations include high-grade glioma and large brain metastases in the context of reirradiation or not among adults and children/AYA.

In recent decades, major technical advances in RT have been implemented and used without rigorous evaluation. PT has been employed for years and the number of treated patients is increasing steadily, driven by the physical advantage of proton beams which allows for a highly conformal dose distribution. The reduction of costs for PT facilities is also encouraging its spread. Nevertheless, even though numerous comparative trials are ongoing, high-quality data from RCT are still scarce in adults. To date, there are no data from RCT in children/AYA. Consequently, available evidence to support the use of PT for the treatment of medulloblastoma for instance, was ranked as moderate [2]. Likewise, the global adoption of IMRT for the treatment of head and neck cancer occurred before robust evidence of its superiority regarding toxicity (xerostomia) was established [46,47]. Of course, promising technologies should be offered as soon as possible, which is why it is crucial to adopt a standardized approach for the implementation of new technologies in radiation oncology. This facilitates its spread and avoid the use of costly techniques with no advantages or those promoted only by marketing arguments of the industry, patients' beliefs, or physician's habits.

The assessment of innovation in RT differs significantly from that in pharmaceuticals, making traditional phase 1–2–3 trials less applicable to RT. RCT have several limitations: (a) technical issues – RT is subject to continuous technical improvements that are outpacing clinical research and may render a technique obsolete by the time a trial concludes (this



situation can be exacerbated by slow recruitment in rare diseases); moreover, achieving technical standardization between centers is difficult due to variability in factors like delineation of target volumes and organs at risk, dose objectives and constraints, treatment planning system, machine and equipment, quality control process, positioning verification; (b) practical issues – radiation oncologists and patients may hesitate to use the standard technique considered outdated while the innovation appears superior; (c) financial issues – RT trials are poorly financed by industry and are challenging to set up; (d) concept issues – RCT embraces the rule of the “winner-takes-all”, the verdict of the trial will apply to all patients but the technique may benefit only a fraction of subjects. This is why other approaches, such as the model-based selection of patients who will benefit from the innovation, have been considered [48]. Patients are selected to be treated with the new technique when the difference between normal tissue complication probabilities (NTCP), evaluated through a comparative planning study, meet a predefined criterion. Nevertheless, this approach cannot be applied with pMBRT. NTCP are built with data from standard homogeneous and normofractionated treatments while pMBRT treatments are heterogeneous, and the use of fractionated regimens is not ideal with pMBRT due to the uncertainty of patient repositioning and the very steep dose gradients involved. Currently, no model is able to provide an equivalent biological dose. pMBRT requires a new mindset in terms of dose prescription and planning. Different dosimetric and geometric parameters may lead to differences in treatment response, a fact that should be considered in the planning and dose prescription. A full understanding of the correlation between the various dosimetric (peak dose, valley dose, PVDR) or geometric parameters (beam width and spacing, proportion between peak and valley widths) and the biological response is lacking. However, significant advancements have been made in the last years to disentangle the parameters that influence the most both tumor control and normal tissue sparing in SFRT. Valley dose appears to be the dominant parameter for tumor control [49]. While valley dose was assumed to be the main parameter influencing normal tissue sparing [50], a recent retrospective evaluation also pointed to peak dose as playing a major role, especially with MBRT [51]. Recently published guidelines on SFRT recommend the use of equivalent uniform dose (EUD) [52,53]. However, the EUD models currently used are based on the linear-quadratic model, which assumes radiation-induced clonogenic cell death is only affected by the radiation dose the cell receives. None of the bystander effect, abscopal effect, vascular effect, and immune modulation – considered major aspects of SFRT irradiations – are modeled in the EUD model, and thus, it may not be suitable for SFRT applications [54]. Alternative radiobiological models considering the above are needed. Whether a modified EUD model would be sufficient to describe the complexity of SFRT is yet to be experimentally determined.

To address some of the aforementioned concerns on the evaluation of RT innovation, we recommend to design adaptive basket trials in early clinical development stages (1 and 2), which allow for iterative improvements to the new technique based on clinical data. Later stages require well-controlled designs to derive strong evidence before routine clinical implementation.

New ways to deliver radiation by changing spatial distribution is a hot topic in radiobiology. pMBRT is a disruptive innovation that challenges the paradigm of uniform dose distribution. What sets pMBRT apart from other SFRT techniques is the unique combination of highly heterogeneous dose distributions and their different radiobiology [55]. The width of MBRT beams is a perfect compromise between the thicker beams in GRID and Lattice, which are mainly palliative, and microbeam RT, with its extreme conditions that restrict its spread. If we consider both the fact that a high enough valley dose is required for good tumor control [49] and the need to keep the peak dose sufficiently low in normal tissues [51], MBRT configurations providing intermediate PVDR could be advantageous among SFRT techniques. This is the case with pMBRT, as the valley dose increases in depth, reaching its maximum at the tumor, while PVDR is usually moderate in normal tissues (around

5–7) [18]. The benefit of using protons also includes their selective energy deposit and their potentially advantageous radiobiology [56].

Beyond brain tumors, pMBRT holds promise for other clinical scenarios. pMBRT could improve local control in other radioresistant tumors when used alone or in addition to standard RT. Additionally, the immunomodulatory effects of MBRT may enhance the anti-tumoral impact of combined immunotherapy/RT treatments. pMBRT could also decrease toxicity in diseases treated by standard RT with a good efficacy but with long-term side effects. The advantages of pMBRT could benefit to non-resected sarcomas, reirradiation cases, high-volume metastatic diseases, pediatric tumors and benign tumors or conditions. These are but a few of the multiple perspectives this innovation offers.

## Conclusion

To conclude, we present here an adapted IDEAL framework suitable for use in a promising new RT technique developed at the Institut Curie, pMBRT. We also propose possible studies on brain tumors in adult and pediatric patients. This systematic method aims to provide high-quality data to facilitate the implementation of a new technology that meets unfulfilled medical needs and to demonstrate its safety and advantages over standard techniques.

## 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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