# Treatment Planning and Delivery Overview of Biology-guided Radiotherapy

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## BACKGROUND

Despite growing clinical evidence suggesting that combination therapy improves survival for patients with multiple tumors[3], clinicians are not able to efficiently treat multiple tumors extracranially, in parallel, during a single session with conventional radiotherapy. As such, approximately 90% of the more than 320,000 patients diagnosed with metastatic disease annually in the United States are not eligible for radiotherapy (RT) due to its limitations, which includes motion management of the tumor and toxicity to healthy tissue. While recent clinical studies demonstrate the benefit of treating many tumors in a single session, today the average is closer to one or two tumors per fraction[4].

Biology-guided radiotherapy or BgRT aims to overcome these limitations by reducing the volume of tissue treated with radiation, and therefore cumulative toxicity, to enable the treatment of oligometastatic and polymetastatic disease, in parallel, in a single session. This paper provides a discussion of BgRT fundamentals, the treatment workflow and its potential in these treatment areas.

## PURPOSE AND SCOPE

### BgRT Defined

BgRT is a method of radiotherapy that relies on the emissions generated by an injected radiotracer to guide the radiotherapy beam during each fraction. As a result, BgRT allows for real-time, tracked dose delivery to tumors, even in those subject to motion.

The purpose of this white paper is to describe BgRT including the workflow, treatment planning and considerations for clinical implementation.

The combination of positron emission tomography (PET) and radiotherapy, in a single machine, brings a paradigm change to conventional image-guided radiotherapies.

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[3] *Palma, David A, et al. "Stereotactic Ablative Radiotherapy versus Standard of Care Palliative Treatment in Patients with Oligometastatic Cancers (SABR-COMET): a Randomised, Phase 2, Open-Label Trial." The Lancet393, no. 10185 (May 18, 2019): 2051–58. https://doi.org/10.1016/s0140-6736(18)32487-5.*

[4] *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624708/*

## INTRODUCTION TO BGRT CLINICAL WORKFLOW

**Figure 1. Schematic of BgRT Clinical Workflow**

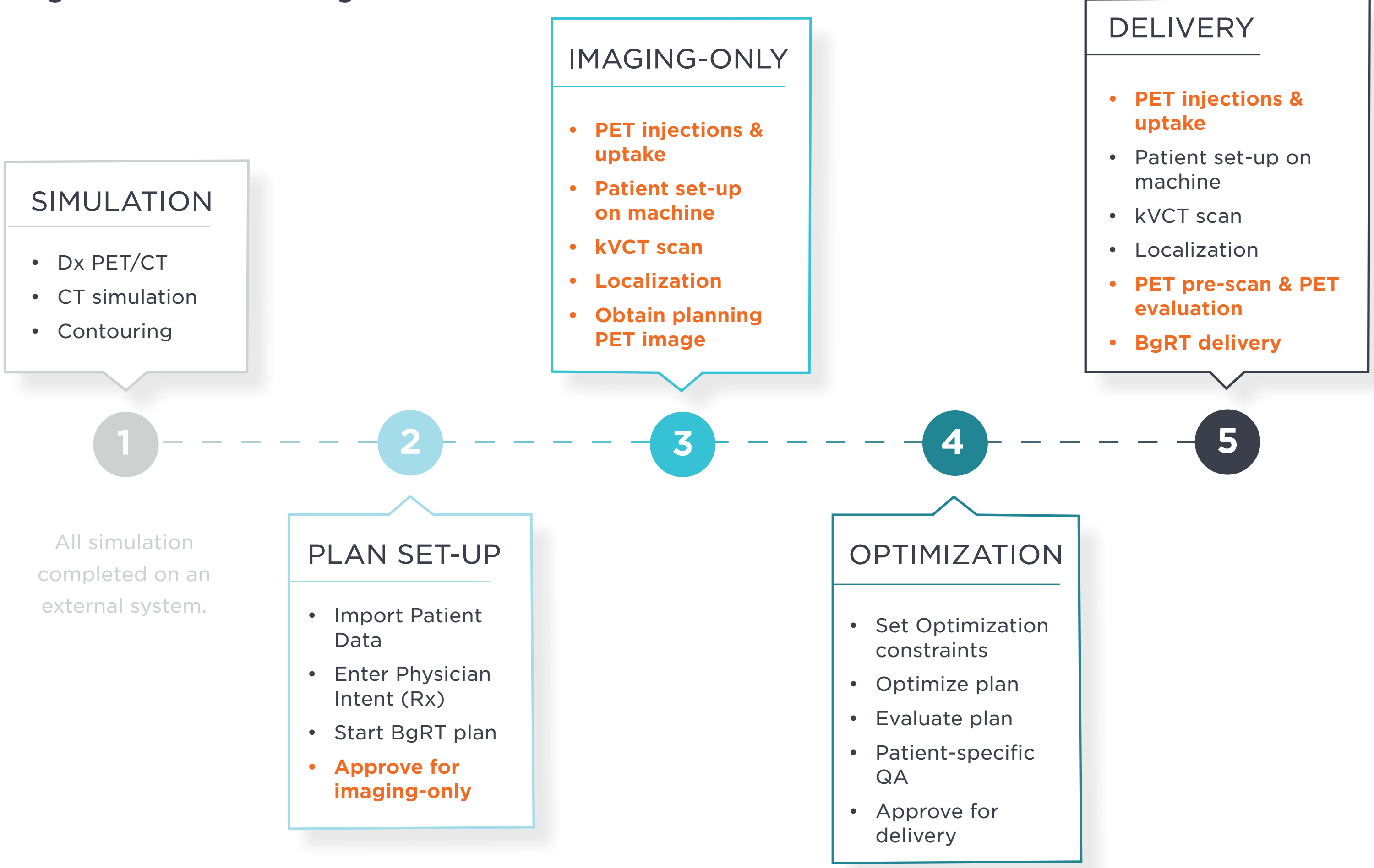


***Figure 1** depicts an overview of the BgRT treatment planning and delivery processes, with steps unique to **BgRT highlighted in orange**.*

### CT Simulation

Similar to conventional RT clinical workflow, BgRT begins with a CT simulation scan for treatment planning followed by contouring the target volumes and organs at risk. These steps are performed on systems separate from the RefleXion platform.

Once completed, the CT simulation scan and treatment planning contours are imported into the RefleXion treatment planning system and the initial physician intent is created.

### Imaging-only Session

The next step in the BgRT clinical workflow is the imaging-only session on the RefleXion machine to acquire both a planning PET image for BgRT treatment planning and a CT scan for target localization.

With BgRT, the patient receives an injection of the commonly available radiotracer fluorodeoxyglucose (FDG). As FDG distributes throughout the body, the tracer accumulates in the tumor(s) just as it does for a diagnostic PET scan. (In the future, BgRT aims to take advantage of a wide array of disease-specific tracers as they become available and validated.)

The imaging-only session is much like a treatment fraction, but without actual radiotherapy delivery. When the patient arrives at the clinic, they receive an injection of FDG and undergo the standard uptake period.

Following the uptake period, the patient is setup on the RefleXion machine for a pretreatment kVCT localization scan that confirms target location. Once completed, the machine acquires the planning PET image. Since the patient has been setup according to the simulation CT used for planning, the planning PET image automatically registers to the simulation CT and serves as a key input for BgRT treatment planning. Note that the imaging-only session requires a full treatment time period.

### Treatment Planning

The workflow for the rest of the treatment planning process is similar to that for conventional radiotherapy. After the BgRT treatment plan has been satisfactorily optimized, evaluated and approved, it is ready to guide treatment delivery. The planning volumes specific to BgRT along with other unique aspects of the BgRT treatment planning process are described below.

### Treatment Delivery

As with the imaging-only session, the patient receives an FDG injection and after the standard uptake period, is moved to the RefleXion machine, setup in the treatment position and a pre-treatment CT scan is performed to confirm target location.

After CT localization, a quick PET pre-scan image is acquired, and evaluated to verify that the BgRT plan can be safely delivered as prescribed. Once this is confirmed, the machine proceeds with treatment.

### FDG Considerations

Because BgRT utilizes positron emissions to guide radiation delivery, the logistics of using FDG during radiotherapy must be considered when integrating this technology into clinical practice. If PET imaging is not already used in the radiation oncology department, coordination and scheduling with the nuclear medicine department is paramount, as is appropriately planning the treatment schedule in the radiation oncology department.

Additionally, since BgRT requires an FDG injection prior to each treatment fraction, it is best suited for hypofractionated therapy. In certain instances, FDG uptake may not be sufficient for tumor localization on the day of treatment, thus necessitating delivery of CT image-guided stereotactic body radiotherapy (SBRT).

## PET IMAGING FOR BGRT VS. DIAGNOSTIC IMAGING

### Emission Detection

With BgRT, emissions generated by PET tracer accumulation in the cancer cells are detected by two 90-degree PET arcs on the machine. These emissions continuously broadcast the location of the tumor – even while in motion.

### Limited Time Sampled PET Images

The PET image that guides BgRT delivery is very different than a diagnostic PET image. Instead of waiting for the generation of a full diagnostic image, the PET arcs on the RefleXion machine continuously acquire limited time sampled (LTS) PET images throughout treatment delivery which reveal the tumor's biological signature.

Using algorithms capable of processing large and complex amounts of data within milliseconds, these LTS PET images are rapidly processed into machine instructions that control the radiation treatment beam to deliver the dose specified by the treatment plan.

**THE CONTINUOUS LIVE FEEDBACK FROM THE TUMOR ITSELF IS A KEY DIFFERENTIATOR BETWEEN IMAGE-GUIDED AND BIOLOGY-GUIDED RADIOTHERAPY.**

## BGRT vs. CONVENTIONAL TREATMENT PLANNING

### Treatment Volumes

While many aspects of BgRT treatment planning are similar to conventional radiotherapy, there are unique differences. In conventional SBRT an internal margin is added to the clinical target volume (CTV) to compensate for internal physiological movements and variation in size, shape, and position of the CTV during therapy.

To account for uncertainties in patient positioning during treatment planning and through all SBRT treatment sessions, a setup margin (SM) is required. The planning target volume (PTV), therefore, includes the CTV with an internal margin (IM) as well as a setup margin (SM) to account for tumor motion and setup uncertainties, respectively.

The construction of the PTV for BgRT is similar, but the margins used to arrive at the treatment volume vary from that of SBRT. BgRT delivers a tracked dose of radiation to a moving tumor target so the entire motion path of the target and the conventional setup margin are not part of the PTV expansion. Instead, a unique biological guidance margin (BgM) that accounts for tracking uncertainties and registration uncertainties between the simulation CT and the planning PET constitutes the PTV expansion.

In contrast to the conventional SBRT PTV, which is fixed relative to the patient anatomy, the BgRT PTV moves within the biology-tracking zone (BTZ), an area unique to BgRT defined by the radiation oncologist at the time of treatment planning.

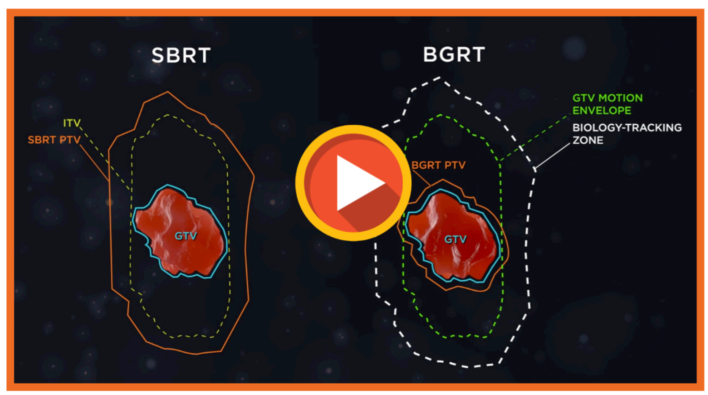


***Figure 2*** *is an animation describing the treatment planning volumes for BgRT.*

The BTZ encompasses the full range of motion of the GTV plus a margin that includes the BgM and the SM. The RefleXion machine uses the BTZ as a limiting factor or safe zone for the delivery of the prescription dose; PET signals arising outside of the BTZ are disregarded by the machine and do not influence the dose delivery.

It's important to note that while radiation delivery can occur anywhere within the BTZ, dose delivery is only prescribed to the moving PTV.

**WHILE DOSE CAN OCCUR ANYWHERE WITHIN THE BTZ, RADIATION IS ONLY PRESCRIBED TO THE SMALLER, MOVING PTV.**

## THE BGRT TREATMENT PLAN

Another unique aspect of BgRT is the output from the treatment planning system. As mentioned previously, the planning PET image acquired on the RefleXion machine is a required input to the treatment planning system.

The BgRT planning process consists of first, defining the desired dose distribution, and subsequently, calculating a mapping from the planning PET image to this desired dose distribution. This mapping is a set of firing filters. The desired dose distribution uses the same types of planning goals and optimization constraints as in conventional radiotherapy.

The BgRT plan is optimized, refined and re-optimized as necessary and the calculated set of firing filters is the output of the treatment planning process. This is fundamentally different from conventional radiotherapy where the treatment plan consists of a set of machine instructions. During BgRT delivery, the firing filters are used in conjunction with the rapidly acquired LTS PET images to control the treatment beam.

## CONCLUSION

BgRT is designed to overcome the current logistical, toxicity and motion management challenges that today limit the use of radiotherapy for metastatic patients.

Through the use of PET emissions for tracking and treating cancer in real time, reducing the treatment volume to allow more dose to treat other tumors, BgRT aims to one day treat multiple tumors in parallel during a single session.