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, 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\(^4\).

SCINTIX\(^\text{™}\) biology-guided radiotherapy from RefleXion may overcome these limitations for patients with tumors in the lung or bone arising from primary or metastatic disease. By reducing the volume of tissue treated with radiation, and therefore cumulative toxicity, SCINTIX therapy aims to enable the treatment of oligometastatic and polymetastatic disease in a single session.

PURPOSE AND SCOPE

Biology-guided Radiotherapy Defined

Biology-guided radiotherapy is a method of radiotherapy that relies on the emissions generated by an injected radiopharmaceutical to control the radiotherapy beam during each fraction. RefleXion’s SCINTIX biology-guided radiotherapy allows for real-time, tracked dose delivery to tumors, even in those subject to motion.

The purpose of this white paper is to describe SCINTIX\(^\text{™}\) biology-guided radiotherapy from RefleXion 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.

---

\(^1\) Principal Clinical Scientist, RefleXion Medical, Inc.
\(^2\) Chief Technology Officer and Founder, RefleXion Medical, Inc.
\(^4\) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624708/
CT Simulation

Similar to conventional RT clinical workflow, SCINTIX biology-guided radiotherapy 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.

Functional Modeling Session

The next step in the SCINTIX therapy clinical workflow is the functional modeling session on the RefleXion machine to acquire both planning PET data for SCINTIX biology-guided radiotherapy treatment planning and a CT scan for target localization. The functional modeling session is much like a treatment fraction, but without actual radiotherapy delivery.

With SCINTIX therapy, the patient receives an injection of the commonly available radiopharmaceutical, fludeoxyglucose F18 (FDG). As FDG distributes throughout the body, the radiopharmaceutical accumulates
in the tumor(s). In the future, SCINTIX therapy aims to take advantage of a wide array of disease-specific radiopharmaceuticals as they become available and validated.

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 planning PET data. Since the patient has been setup according to the simulation CT used for planning, the planning PET data automatically registers to the simulation CT and serves as a key input for SCINTIX therapy treatment planning. Note that the functional modeling 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 SCINTIX biology-guided radiotherapy treatment plan has been satisfactorily optimized, evaluated and approved, it is ready to guide treatment delivery. The planning volumes specific to SCINTIX therapy along with other unique aspects of the treatment planning process are described below.

**Treatment Delivery**

As with the functional modeling 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 is acquired, and evaluated to verify that the SCINTIX biology-guided radiotherapy plan can be safely delivered as prescribed. Once this is confirmed, the machine proceeds with treatment.

**FDG Considerations**

Because SCINTIX technology utilizes positron emissions to control 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 SCINTIX therapy 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 FOR SCINTIX BIOLOGY-GUIDED RADIOTHERAPY VS. DIAGNOSTIC IMAGING**

**Emission Detection**

With SCINTIX technology, emissions generated by PET radiopharmaceutical accumulation in the cancer cells are detected by two 90-degree PET arcs on the machine. These emissions stream live continuously - even while the tumor is in motion. The X1 constructs a map from the detected emissions data that controls where to deliver beamlets of radiation during treatment delivery.
Using algorithms capable of processing large and complex amounts of data within milliseconds, these data are rapidly processed into machine instructions that control the radiation treatment beam to deliver the dose specified by the treatment plan.

CONTINUOUS LIVE FEEDBACK FROM THE TUMOR ITSELF DIFFERENTIATES SCINTIX THERAPY FROM OTHER EXTERNAL-BEAM RADIOTHERAPY

SCINTIX THERAPY vs. CONVENTIONAL TREATMENT PLANNING

Treatment Volumes

While many aspects of SCINTIX therapy 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 conventional radiotherapy treatment sessions, a setup margin (SM) is required. The planning target volume (PTV), therefore, includes the CTV with an internal margin (IM) and as a setup margin (SM) to account for tumor motion and setup uncertainties, respectively.

The construction of the PTV for SCINTIX biology-guided radiotherapy is similar, but the margins used to arrive at the treatment volume vary from that of SBRT. SCINTIX therapy 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 data constitute the PTV expansion.

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

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, not to the entire BTZ.

WITH SCINTIX THERAPY, RADIATION IS ONLY PRESCRIBED TO THE SMALLER, MOVING PTV.

Figure 2 is an animation describing the treatment planning volumes for SCINTIX biology-guided radiotherapy.
Another unique aspect of SCINTIX biology-guided radiotherapy is the output from the treatment planning system. As mentioned previously, the planning PET data acquired on the RefleXion machine is a required input to the treatment planning system.

The SCINTIX biology-guided radiotherapy planning process consists of first, defining the desired dose distribution, and subsequently, generating a mapping from the planning PET data to create the 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 SCINTIX biology-guided radiotherapy 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 SCINTIX therapy delivery, the firing filters are used in conjunction with the rapidly acquired PET data to control the treatment beam.

CONCLUSION

SCINTIX™ biology-guided radiotherapy from RefleXion is the first and only therapy to use emissions from the cancer itself to control treatment delivery. This breakthrough technology is designed to overcome the current logistical, toxicity and motion management challenges that today limit the use of radiotherapy for metastatic patients.