

# **RESEARCH PROJECT**

**“Impact of partial stereotactic body radiotherapy on hypoxic segments of large-volume and unresectable tumors (SBRT-LATTICE-PATHY) – a prospective phase II study”**

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## ABSTRACT

**Introduction:** In oncology, the treatment of patients with bulky tumors can be highly challenging because of tumor resistance, reduced performance status, and poor treatment tolerability. Even for palliation, with lower doses, radiotherapy poses problems related to the need for larger treatment fields and increased risks of toxicity, with limited clinical benefit. New radiotherapy concepts have emerged and evolved, such as spatial radiotherapy techniques delivering “islands” of high radiation dose to reduced volumes within the tumor (SBRT-LATTICE), as well as to hypoxic areas (PATHY), with promising results in reducing tumor volume, possibly explained by local and distant immunologic effects. **Objectives:** To evaluate the impact of the SBRT-LATTICE-PATHY technique on tumor volume reduction and local control. **Methods:** At least 20 patients aged 18 years or older will be recruited, with histologically confirmed malignant or benign neoplasms in which radiotherapy has a role in treatment according to the international literature, tumor volume  $\geq 340 \text{ cm}^3$  and/or diameter  $\geq 7 \text{ cm}$ , *Eastern Cooperative Oncology Group – performance status* (ECOG-PS)  $\leq 2$ , and *Palliative Prognostic Index* (PPI) score  $\leq 2$ , with controlled CNS metastatic disease when present and up to 5 extracranial metastases measuring up to 5 cm each. Treatment will consist of a single fraction of 24 Gy delivered to 1-cm diameter vertices spaced 3 to 6 cm apart within a predefined area of intratumoral hypoxia.

Keywords: stereotactic radiotherapy; LATTICE; partial irradiation; bulky tumors.

## 1. INTRODUCTION

In recent decades, we have witnessed major developments in oncologic treatment. As tumor and immunologic signaling pathways become increasingly better understood, new modalities such as targeted therapy and immunotherapy have gained growing relevance in cancer treatment protocols across various disease sites, with positive outcomes even in terms of overall survival.

<sup>1</sup>The advent of new technologies such as radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) has enabled the delivery of high, ablative radiation doses to tumors in a small number of fractions, generating not only antineoplastic effects and vascular occlusion within the tumor microenvironment, but also innate and adaptive immune response mechanisms, such as increased antigen exposure, antigen presentation by dendritic cells, and cytotoxic functions of CD8<sup>+</sup> T lymphocytes<sup>2</sup>. These mechanisms, together with increased production of inflammatory cytokines (TNF, IL-1 $\alpha$ , IL-6) and reactive oxygen species, help explain cell death in non-irradiated areas, known as the local *bystander* effect and the distant abscopal effect.<sup>3 4 5</sup>

However, SRS/SBRT treatments have historically remained quite limited by tumor volume and are not considered feasible and safe for tumors larger than 5 cm in diameter due to tolerance constraints of adjacent normal tissues.<sup>6</sup> This prompted the search for new radiation delivery techniques for these bulky lesions, which are often considered unresectable, in the setting of advanced disease with no possibility of cure. In many cases, even conventional palliative-dose radiotherapy is not feasible because it would require very large treatment fields, thereby increasing irradiation of normal tissues or organs at risk (OARs).

It is in this context that Spatially Fractionated Radiotherapy (SFRT) emerged, characterized by non-uniform irradiation of the tumor volume, combining protection of normal tissues with local and distant tumor response in the presence of metastases. The original technique, known as GRID therapy, was developed in the early 20th century using perforated collimation blocks of different sizes and hole diameters, but in a two-dimensional (2D) setting, resulting in high irradiation outside the intended clinical volume. With the advent of the three-dimensional (3D) era, the LATTICE technique (LRT) was developed, characterized by the definition of small spherical

volumes within the tumor lesion, called vertices, where high doses of radiation are delivered, with promising results regarding local tumor control and no increase in toxicity<sup>7 8</sup>. This technique can be combined with SBRT requirements to ensure greater accuracy and safety in dose delivery, which involves specific criteria for positioning, immobilization devices, image acquisition, planning, position verification, and treatment adjustments using image-guided radiotherapy (IGRT).

Regarding histologies, some studies have demonstrated benefit in local control and tumor volume reduction, with clinical response rates ranging from 50% to 100% in some radioresistant tumors such as soft tissue sarcoma, osteosarcoma, and melanoma, but also in radiosensitive tumors such as head and neck cancers.<sup>9 10</sup>

It is important to understand that the tumor environment is divided into specific regions according to the level of tissue/cellular oxygenation. A study by *Ikeda et al.*<sup>11</sup> demonstrated that the hypoxic tumor cell region within the tumor induces decreased gene expression of a potent anti-angiogenic factor called sFlt-1. sFlt-1 has the ability to bind VEGF (vascular endothelial growth factor) in the extracellular environment with greater affinity than VEGF binding to its receptor (VEGFR), thereby preventing the formation of new vascular endothelium. Under hypoxic conditions, VEGF action is greater at the expense of sFlt-1, culminating in neoangiogenesis, which is fundamental to tumor cell survival. Based on this premise, the hypoxic tumor region became a subject of investigation as a possible target for radiotherapy to further promote *bystander* and abscopal effects. A U.S. study demonstrated this potential through *in vitro* experiments showing that irradiation of hypoxic lung cancer cells increased sFlt-1 levels compared with normoxic or non-irradiated cells.<sup>12</sup>

Based on this, a retrospective study was carried out<sup>13</sup> evaluating the use of SBRT-PATHY (stereotactic body radiotherapy for partial tumor irradiation in a hypoxic segment) in large-volume tumors (mean volume 179.8 cm<sup>3</sup>) of various histologies (adenocarcinoma, squamous cell carcinoma, melanoma, and renal cell carcinoma), with different primary disease sites (predominantly pulmonary). Although no imaging method is fully effective for locating the hypoxic tumor region, the treatment volume BTV (*bystander target volume*) was defined as the

band located between the necrotic tumor center and the peripheral hypermetabolic/hypervascularized segment (with the aid of contrast-enhanced computed tomography and 18F-FDG-PET-CT). The dose used was up to 3 fractions of 10 Gy, with the possibility of retreatment if, after 1 month of reassessment of the first treatment course, the BTV could still be visualized. The local clinical response rate was 96% and the distant response rate was 52%; after 4 months, median tumor reduction was 70% (range 30–100%), and no patient experienced acute or late toxicity.

In Brazil, as in other low- and middle-income countries, cancer treatment is severely affected by scarce healthcare resources, with shortages of qualified professionals and limited diagnostic and treatment technology. This results in prolonged waiting times and loss of the “optimal” treatment window, and many patients arrive at oncology services with advanced disease and no remaining possibility of curative treatment.<sup>14</sup> Many resources are therefore directed toward palliative treatments and end-of-life care. Thus, treating bulky disease with good expectations of clinical response may offer hope in reducing the impact caused by these shortcomings.

Given the lack of stronger evidence in the literature, it is necessary to conduct a prospective study to evaluate the importance of using SBRT-LATTICE-PATHY for the radiotherapeutic treatment of bulky tumors that would currently be considered untreatable by standard techniques. In the present study, there will be an opportunity to combine SBRT and LATTICE techniques while incorporating the concept of irradiating hypoxic tissues as potential modulators of abscopal and *bystander* effects, delivering focal partial treatment to vertex regions without the need to irradiate the entire tissue volume, thereby further improving safety with regard to possible toxicities.

## **2. OBJECTIVES**

### **2.1. Primary objective**

To evaluate the impact of SBRT-LATTICE-PATHY on tumor volume reduction and local control.

### **2.2. Secondary objectives**

To evaluate overall survival, progression-free survival, incidence of acute and late side effects, and impact on quality of life.

## **3. HYPOTHESIS(ES)**

SBRT-LATTICE-PATHY has a positive impact on reducing bulky tumor volume, with improved local control.

## **4. STUDY RATIONALE**

There is a need to obtain more robust evidence on SBRT-LATTICE-PATHY as a promising modality for treating patients with large-volume tumors, which would generally be considered untreatable and for whom only exclusive palliative/clinical care would be offered.

## **5. MATERIALS AND METHODS**

### **5.1. Study design**

This is a prospective, single-arm, non-randomized phase II clinical trial.

### **5.2. Sample size calculation**

This will be a convenience sample. We plan to include at least 20 (twenty) patients over a 2-year period.

### **5.3. Ethical considerations of the study**

The study was designed in accordance with the Regulatory Guidelines and Standards for Research Involving Human Subjects and will be submitted to the institution's Ethics Committee. The study will first be approved by the internal Ethics Committee of the Cancer Institute of the State of São Paulo (ICESP) and InRad, and subsequently by the Research Ethics Committee of the University of São Paulo School of Medicine.

The study poses a low risk to participating patients, according to retrospective studies and a phase I study already published.<sup>15</sup>

Among the possible side effects (according to CTCAE v5.0 classification):

**1. Common side effects (>10%):**

- nausea/vomiting (grade 1-2)
- diarrhea (grade 1-2)
- fatigue (grade 1-2)
- pain (grade 1-2)
- dysuria / urinary frequency (grade 1-2)
- anxiety (grade 1-2)
- radiodermatitis (grade 1)

**2. Uncommon side effects (1-10%)**

- worsening respiratory pattern due to radiation pneumonitis (grade 1-2)
- radiodermatitis (grade  $\geq 2$ )

**3. Rare side effects (< 1%)**

- tumor lysis syndrome
- dysuria and urinary frequency ( $\geq$  grade 3)
- worsening respiratory pattern due to radiation pneumonitis ( $\geq$  grade 3)
- reduced renal function ( $\geq$  grade 3)
- reduced hepatic function ( $\geq$  grade 3)
- nausea/vomiting ( $\geq$  grade 3)

- diarrhea ( $\geq$  grade 3)
  - fatigue ( $\geq$  grade 3)
  - pain ( $\geq$  grade 3)
  - anxiety ( $\geq$  grade 3)
  - radiation cystitis
  - radiation proctitis/colitis
- 4.** Side effects not described in the literature, but with a very rare potential to occur ( $< 0.1\%$ )
- grade 4 intestinal toxicities (perforations, necroses, fistulas)
  - rupture of large arterial and/or venous blood vessels
  - necrosis of healthy skin and/or soft tissues
  - bone necrosis (osteoradionecrosis)
  - chronic joint dysfunction (restriction, fibrosis, necrosis)
  - pneumothorax (due to airway perforation)
  - radiation-induced changes to the spinal cord and/or cauda equina and/or nerve plexuses and/or peripheral nerves
  - grade 5 toxicity

In the event of severe unexpected side effects, the patient will be referred to the emergency department for evaluation, at the physician's discretion.

### **5.3.1 Informed Consent Form (ICF)**

An informed consent form will be applied to all participating patients.

## **5.4. Context for conducting the study procedures**

- a)** Cases of patients potentially eligible for the study, treated exclusively at the Cancer Institute of the State of São Paulo (ICESP), will be referred to the radiotherapy service at InRad (Institute of Radiology).

- b)** An outpatient consultation will be carried out to verify eligibility criteria and administer the informed consent form and the pre-treatment quality-of-life assessment questionnaire (EORTC QLC-C30). Planning computed tomography (CT) will then be scheduled;
- c)** Planning computed tomography will be performed according to the study procedures protocol;
- d)** CT images will be sent to the Eclipse™ v. 16.1 planning system (Varian™);
- e)** Target structures and organs at risk (OARs) will be contoured by the physician according to the study procedures protocol;
- f)** Case planning will be performed by the physicist according to the study procedures protocol;
- g)** Planning will be evaluated and approved by the physician in accordance with the study procedures protocol;
- h)** Quality control procedures will be performed according to the study procedures protocol;
- i)** The patient will be scheduled for treatment;
- j)** Treatment will be delivered according to the study procedures protocols;
- k)** Outpatient follow-up visits will take place at 15 days, 1 month, 3 months, 6 months, 9 months, and 12 months.
- l)** Follow-up CT scans (of regions known to be involved by disease at study entry) will be performed at 1, 3, 6, 9, and 12 months. For other locations, imaging will be performed only if clinically suspected.
- m)** Follow-up CT images will be imported into the Eclipse™ v. 16.1 system (Varian™) for fusion with the planning CT, contouring, and evaluation of the treated lesion volume. The volume of metastatic lesions will be quantified by mean volume (based on the dimensions of the x, y, and z axes).

## 5.5. Participants

### 5.5.1. Eligibility criteria

- Inclusion criteria:
  - . age  $> 18$  years;
  - . Eastern Cooperative Oncology Group performance status scale (ECOG)  $\leq 2$ ;
  - . benign and malignant tumors for which the use of radiotherapy is well established in the literature;
  - . tumors  $\geq 340 \text{ cm}^3$  or with largest diameter  $\geq 7 \text{ cm}$ ;
  - . no indication for any other type of treatment due to lack of proven clinical benefit (surgery, chemotherapy, standard radiotherapy, immunotherapy, targeted therapy, etc.);
  - . PPI (*Palliative Prognostic Index*)  $\leq 2$ ;
  - . metastatic disease in the central nervous system (CNS), if present, must be controlled (up to 3 metastases of up to 1 cm each);
  - . up to 5 extracranial distant metastases (nodal or extra-nodal)  $\leq 5 \text{ cm}$ ;
  - . signature of the Informed Consent Form (ICF);
- Exclusion criteria:
  - . cases in which tumor volume and/or the patient's clinical condition make adequate immobilization/simulation unfeasible
  - . prior local radiotherapy
  - . pregnant patients
  - . autoimmune diseases
  - . genetic instability syndromes
  - . ongoing systemic therapy
  - . renal insufficiency that prevents the use of iodinated contrast

### **5.5.2.Source and methods of participant selection and recruitment**

Patients who may be eligible for the study will be referred on an outpatient basis by the clinical oncology or oncologic surgery departments of ICESP to the radiotherapy department. Referrals will be directed through triage to the radiotherapy service at InRad. Clinical data are stored in the electronic medical record in the Tasy® system, with support from MOSAIQ™.

Referred cases will be evaluated by the investigator physician for recruitment into the study, according to the inclusion criteria.

## **5.6. Outcome(s) analyzed**

### **5.6.1.Primary outcomes**

- tumor volume reduction rate (at 1, 3, 6, 9, and 12 months), expressed as a percentage;
- local control (defined as the time interval from treatment to tumor progression at the treatment site);

### **5.6.2.Secondary outcomes**

- overall survival (defined as the time interval from treatment to death from any cause);
- progression-free survival (defined as the time interval from treatment to local or distant disease progression);
- incidence of acute side effects at 15 days, 1 month, and 3 months;
- incidence of late side effects at 6, 9, and 12 months;
- impact on quality of life, according to the EORTC QLC-C30, before treatment and after treatment at 1, 3, 6, 9, and 12 months.

## **5.7. Variables collected from patients**

- a) full name
- b) age
- c) HC registration number
- d) ICD-10

- e) sex
- f) histology
- g) histologic grade
- h) main tumor volume (before treatment and after treatment at 1, 3, 6, 9, and 12 months)
- i) location of the main tumor disease
- j) number of metastases
- k) location of metastases
- l) metastatic lesion volume (before treatment and after treatment at 1, 3, 6, 9, and 12 months)
- m) treatment date
- n) individual coverage (V100%) of the z\_spheres
- o) dose assessment in nearby OARs according to tolerance dose tables (*constraints*) described in the procedures protocol
- p) acute and late toxicity scores, according to CTCAE v5.0
- q) quality-of-life score according to the EORTC QLC-C30

## 5.8. Statistical analyses

### 5.8.1.Descriptive analysis

- a) Assessment at 1, 3, 6, 9, and 12 months:
  - tumor volume reduction
  - local control
  - overall survival
  - progression-free survival
  - acute side effects (1 and 3 months) and late side effects (6, 9, and 12 months)
  - impact on quality of life

### 5.8.2.Inferential analysis

Comparison between groups will be performed using SigmaPlot™ 15.0, by means of the t-test or U test (Mann-Whitney), depending on sample distribution, in order to verify statistically significant differences, considering a 95% confidence interval and  $p=0.05$ :

- **groups:** tumor volume (up to 1000 cm<sup>3</sup> versus > 1000 cm<sup>3</sup>); epithelial versus mesenchymal histologies; histologic grade (1 vs 2-3).
- **variables:** tumor volume reduction rate (at 1, 3, 6, 9, and 12 months) as a percentage; local control at 1, 3, 6, 9, and 12 months; mean progression-free survival at 1, 3, 6, 9, and 12 months.
- **groups:** number of metastases (none versus 1-5 metastases); ECOG (0-1 versus 2)
- **variables:** local control at 1, 3, 6, 9, and 12 months; mean progression-free survival at 1, 3, 6, 9, and 12 months;

## **5.9. Measures to minimize potential sources of bias**

The most likely bias in this study is selection bias. Inclusion and exclusion criteria will be followed to minimize it.

## **5.10. Management of collected data**

Data will be stored in spreadsheets and transferred to the Sigma Plot™ 15.0 statistical system for analysis according to the study design.

## **5.11. Treatment Protocol**

### **5.11.1. Simulation/Planning:**

#### **5.11.1.1. Accessories / Positioning:**

- dependent on treatment location
- Head and Neck: supine position, SRS mask, shoulder pull-down device

- Thorax/abdomen/pelvis: supine position, arms raised, W base, thigh and foot support (SBRT)
- Back: prone position, Vac-Lok, arms up.
- Limbs: supine/prone position, Vac-Lok or immobilization mask for limbs

#### 5.11.1.2. **Simulation technique:**

- Acquisition limits will be determined by the physician according to the anatomic site.
- FOV restricted to the area of interest.
- 2.5/2.5 mm slices, with iodinated contrast 1.0 ml/kg (if possible);
- Mark the CT localization isocenter on the patient's skin or mask (if applicable).
- The acquired images will be sent to the Eclipse® planning system for physician contouring.
- CT with and without IV contrast 1.0 ml/kg – arterial and venous phases

#### **- If the site has respiratory motion:**

- Simulation with motion control is possible [deep inspiration breath hold (DIBH) or respiratory *gating*]. If necessary, use ABDOMINAL COMPRESSION.
  - check motion on the linear accelerator (LINAC) with **fluoroscopy**
    - if  $> 5$  mm – adjust abdominal compression or ABORT the procedure.
    - if  $\leq 5$  mm – perform 4D CT or equivalent.
  - if RPM / respiratory *gating* is used, perform CT and select the expiratory pause phase (generally 30–70%)
    - if DIBH is chosen, perform CT at maximum inspiration.

### 5.11.1.3. Contouring:

#### a) Treatment Volumes:

- . **GTV<sub>insp</sub>**: gross tumor volume (GTV) in the inspiratory phase (if there is respiratory motion)
- . **GTV<sub>exp</sub>**: GTV in the expiratory phase (if there is respiratory motion)
- . **GTV<sub>inter</sub>**: intersection between GTV<sub>insp</sub> and GTV<sub>exp</sub>
- . **S-GTV**: GTV<sub>inter</sub> (if there is respiratory motion) or GTV minus an internal margin of 5 to 10 mm (depending on the need in each case, for greater safety)
- . **NV**: tumor necrosis volume (central tumor area of hypoattenuation)
- . **BV**: *bystander* volume, defined as the 2-cm-thick ring around the NV
- . **z\_spheres**: draw 1-cm spheres (diameter) using the grid tool:
  - each sphere must be individualized (z\_sphere1; z\_sphere2; z\_sphere3, etc.)
  - the spheres should be spaced approximately 3 cm apart from center to center in all planes (axial, sagittal, and coronal);
  - the sphere borders must MANDATORILY remain within the S-GTV
  - there must be at least partial intersection between the sphere volume and the BTV
  - the sphere borders must MANDATORILY be 1 cm away from critical OARs;
  - there is no margin for the z\_spheres
  - the distances do not need to be exact
  - total z\_spheres: sum of all z\_spheres.
  - z\_IC (*inner control*): total z\_spheres + 0.5 cm
  - z\_MC (*middle control*): total z\_spheres + 1 cm

- z\_OC (*outer control*): total z\_spheres + 3 cm

- Body-spheres: Body (limited to 10 cm above and below the GTV) – total z\_spheres

**b) OARs:**

- Contouring of OARs

- For organs at risk close to the GTV, apply a 1-cm PRV (*Planning Organ at Risk Volume*) margin.

- If there is intersection between the OAR PRV and z\_spheres:

- evaluate the possibility of shifting the z\_spheres

- evaluate the possibility of removing the z\_sphere that intersected the OAR PRV;

- if the options above are not possible, consider **ABORTING TREATMENT**.

**5.11.1.4. Planning**

- Use the VMAT technique, with 6FFF or 10FFF energy

- Objectives:

- Coverage: z\_spheres (individually): 100% dose  $\geq$  50% volume

- The 30%-40% isodose lines should remain within the GTV, between the z\_spheres

- *Constraints:*

CORSAIR <sup>16</sup> / Timmerman et al. <sup>17</sup>	
OAR	Constraints
Brain-GTV	D50% < 5Gy D10cc < 12Gy
Brainstem	D0,035cc < 15Gy (mandatory) D0,035cc < 10Gy (ideal)

Cochlea	Dmed < 9Gy (mandatory) Dmed < 4Gy (ideal) Dmax < 12Gy
Eye	Dmax < 8Gy
Optic nerve	D0,035 < 10Gy (mandatory) D0,035 < 8Gy (ideal)
Retina (posterior eye)	Dmax < 5Gy
Lens	D0,035 < 1,5Gy
Lacrimal gland	Dmax < 5Gy
Pituitary gland	Dmed < 9Gy
Spinal cord	V 12,4Gy < 0,035cc (ideal) V 14Gy < 0,035cc (mandatory)
Partial spinal cord	V 10Gy < 10%
Esophagus	D0,1cc < 15,4Gy (mandatory) V16 < 0,03 cc V11,9 < 5 cc (ideal)
Stomach	D0,1cc < 12,4Gy (mandatory) D10cc < 11,2Gy (ideal)
Brachial plexus	V17,5 < 0,03cc V14 < 3cc
Heart / Pericardium	V22 < 0,03cc V16 < 15cc
Great vessels	V37 < 0,03cc V31 < 10cc
Larynx	V10,5Gy < 4cc V20,2Gy < 0,035cc

Airways (trachea / larynx / bronchi)	V20,2 < 0,03cc V10,5 < 4cc
Total lung - ITV	V7,4 < 1000cc V20Gy < 10% (ideal) V20Gy < 15% (mandatory) D1500cc < 7Gy Dmed < 8Gy
Chest wall	D0,01cc < 30Gy V22 < 1cm <sup>3</sup>
Skin	V26 < 0,03cc V23 < 10cc
Stomach	V16 < 0,03cc V11,2 < 10cc
Liver	D700cc < 9,1Gy V12Gy < 30% V5Gy < 50% V2,5Gy < 70%
Common bile duct	D0,1cc < 30Gy
Duodenum	V16 < 0,03cc D0,1cc < 12,4Gy D10cc < 9Gy V11,2 < 5cc
Jejunum and ileum	V15,4 < 0,03cc V11,9 < 5cc
Colon	V18,4 < 0,03cc V14,3 < 20cc

Sigmoid colon	D20cc < 18,4Gy (mandatory) D20cc < 14Gy (ideal)
Rectum	V18,4 < 0,03cc V14,3 < 20cc
Renal hilum and vascular trunk	V10,6 < 2/3volume
Total kidney (cortex)	V8,4Gy < 200cc V10Gy < 33%
Bladder	D0,1cc < 18,4Gy V11,4 < 15cm <sup>3</sup>
Penile bulb	D0,035cc < 34Gy (mandatory) D3cc < 14Gy (ideal)
Sacral plexus	V18 < 0,03cc V14,4 < 5cc
Cauda equina	V16 < 0,03cc V14 < 5cc
Femoral head	D10cc<14Gy

### 5.11.2. Treatment

#### 5.11.2.1. Dose

- SBRT-LATTICE-PATHY: 1 x 24 Gy to the vertices (z\_spheres)

#### 5.11.2.2. Positioning

- a) Place the patient on the LINAC couch using the same positioning/accessories and parameters used in the simulation CT;
- b) Align the room lasers with the marks on the patient's skin (set-up)
- c) Position the stereotactic accessory and adjust the room lasers
- d) IGRT

- Daily position verification using Cone Beam CT (CBCT);

#### **5.11.2.3. Cone Beam CT workflow:**

##### **a) Daily image acquisition**

##### **i. Acquisition modes for sites with respiratory motion:**

- WITHOUT ABDOMINAL COMPRESSION with motion control:

acquire the image during the expiratory pause phase of the respiratory cycle (patient breathing freely).

- DIBH, WITHOUT COMPRESSION with motion control: acquire the image at maximum inspiration

- WITH ABDOMINAL COMPRESSION: acquire the image during free breathing

##### **b) Fusion with planning CT**

- fuse using bony parameters – restrict the VOI (*volume of interest*) to regions of greater fixation (long bones, thoracic/lumbar vertebrae, posterior costal arches)

##### **c) Fine adjustments may be made by restricting the VOI to soft tissues;**

- perform fusion using nearby organs: liver, kidney, etc.
- ensure that the tumor moves within the PTV margin (if applicable)

**If positioning changes greater than 10 mm or 3 degrees are observed, consider repositioning.**

#### **5.11.2.4. Dose delivery.**

##### **a) WITH ABDOMINAL COMPRESSION: free breathing**

##### **b) WITHOUT ABDOMINAL COMPRESSION: free breathing, but in sites with respiratory motion, the dose is delivered during the expiratory pause phase of the respiratory cycle (free-breathing/gating/RPM mode) or deep inspiration breath hold (DIBH).**

## 6. COSTS

The study does not involve additional costs beyond those of the treatment itself, since the LATTICE-SBRT modality is already performed in the Radiotherapy Department of the Institute of Radiology (InRad).

## 7. TIMELINE

Stages	1st-3rd month	4th-12th month	13th-18th month	19th-24th month	25th-30th month	31st-36th month	37th-42nd month	43rd-48th month
Development of the Research Project								
Submit the project to the Ethics Committee.								
Recruitment and treatment period								
Data analysis								
Preparation of the final work								

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