Technical challenges of linac-based stereotactic ablative body radiotherapy: short review for non-radiation oncologists

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Abstract: Stereotactic ablative radiotherapy (SABR) is a radiation technique delivering high doses of radiation in a small number of treatments, to extracranial targets. It is standard of care in patients with inoperable early stage non-small cell lung cancer, and it is increasingly used in patients with oligometastatic disease. The main advantage of SABR is a steep dose gradient, allowing delivery of high biologically effective doses to the target, while minimizing irradiation exposure of the neighboring normal tissues. This results in high rates of local control of the treated target and minimal toxicity risks, and minimal impact on the quality of life of the patients. However, it requires high precision, accuracy and reproducibility during the entire process, from simulation to treatment planning and treatment delivery. This article will focus on general principles of SABR treatment planning and delivery, with emphasis on the strategies to reduce errors related to immobilization, respiratory management and treatment verification.

Keywords: Stereotactic ablative body radiotherapy technique (SABR technique); respiratory motion management; treatment verification

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Introduction

Stereotactic ablative body radiotherapy (SABR) or stereotactic body radiotherapy (SBRT) is a radiation technique that delivers very high doses of radiation (7.5–24 Gy per fraction), in a small number of treatments (1-8), to extra-cranial targets. SABR is currently the standard of care for patients with inoperable early stage non-small cell lung cancer (i.e., inoperable because of medical comorbidities) or for those who opt against surgery (1,2). In these patients, SABR results in long-term survival outcomes that are similar to surgery, with low risk of toxicity and little detriment to quality of life (3-6). SABR is also increasingly being used in patients with oligometastatic, oligo-recurrent or oligoprogressive malignancies.

SABR is also increasingly being used in patients with oligometastatic, oligo-recurrent or oligoprogressive malignancies. The concept of oligometastatic disease was initially defined in 1995 by Hellman and Weichselbaum (7). It represents an intermediate state between the localized disease and wide spread metastatic disease, with more indolent course. Resection or ablative treatments of all sites of known limited metastatic disease could result in prolonged disease free survival with the potential for cure in these patients (8). The most commonly accepted definition of oligometastatic disease refers to less than 5 metastases in less than 3 organs. While a consensus definition of the oligometastatic state has not been reached, some have further subdivided patients based on the temporal development or progression of metastases in regards to...
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... presents the main indications of SABR to reduce the motion of the targets/... usually use vacuum cushions to... It is suitable for patients who are poor candidates for surgery or other ablative techniques.

However, the steep dose gradient achieved with SABR also represents a technical challenge, as set-up errors, intra-fraction motion and respiratory motion of the target can lead to under-dosing of the target and/or unwanted irradiation of normal tissues, and therefore increase the risk of toxicity, particularly with the relatively high biologically effective doses that are used. This can be especially critical for targets situated near the spinal cord, duodenum/stomach or central thoracic structures. Therefore, all efforts should be made to reduce these uncertainties. Currently available practice guidelines from the American College of Radiology (ACR) and American Society of Radiation Oncology (ASTRO), and American Association of Physicists in Medicine (AAPM), emphasize that the overall process of SABR requires strict protocols in treatment simulation, planning and delivery.

In addition, while modern technologies allow for SABR to be delivered in a course of days as opposed to weeks (with conventional radiotherapy), the duration of the individual treatments (with additional effort required for precise immobilization, and monitoring of the patient and/or target before and during treatment) remains long (15–60 minutes) compared to the conventional radiation techniques (generally on the order of 5–15 minutes). Therefore, comfort and compliance of patients undergoing SABR are of paramount importance. Table 3 presents a synopsis of the main requirements for SABR.

General principles of SABR treatment planning and delivery will be presented in the next sections, with emphasis on the strategies to reduce errors related to immobilization, respiratory management and treatment verification.

**Immobilization**

Comfortable immobilization of the patient reduces the risk of inter and intra-fraction errors. Several immobilization devices available are commercially available, with reported repositioning accuracy between 0.3–5.6 mm. Body frames (Figure 1A) usually use vacuum cushions to physically immobilize patients, while maintaining comfort. Additionally, some groups use abdominal compression devices (Figure 1B) to reduce the motion of the targets/ organs at risk in areas with known large motion (lower lungs, upper abdomen); however, abdominal compression is often uncomfortable and has been shown to deform anatomy, depending on the positioning and the pressure...
applied. Furthermore, abdominal compression cannot be used for patients with abdominal co-morbidities, such as aortic aneurysms or gastrostomies. Some groups from Scandinavia advocate no immobilization, favoring patient comfort. However, while current imaging systems allow for detection and correction in patient positioning, they cannot replace proper immobilization of the patients. Accurate immobilization is critical in patient undergoing spine SBRT: studies assessing different immobilization devices, suggest that the use of semirigid vacuum immobilization (body frame) is associated with the least intra-fraction errors (compared to evacuated cushion or thermoplastic S-frames) (24).

Generally, patients are set-up in a dorsal decubitus position, with their arms above the head (unless treating a target in the head and neck region (Figure 1B) or lower abdomen or pelvis). Removing the arms from the beam entry is generally necessary, since imprecise arm positioning will affect the accuracy of dosimetry; therefore, elevating the arms allows for more flexibility in the choice of beam directions. However, this position can be associated with positional pain in the shoulders and upper back, especially in the context of long treatment times. Such discomfort can cause patient motion during treatment, and therefore increase the risk of errors in dose delivered.

### Simulation

Simulation is an essential part of the radiotherapy process.
For SABR, most centers will use CT scans for simulation, with few using MRIs or PET-CT at the time of simulation. Diagnostic imaging (including PET-CT and MRI) obtained prior to or after simulation can be registered to the images obtained at simulation (25). If feasible, attempts to position the patient for diagnostic imaging similarly (i.e., using a flat board) to the position in simulation will facilitate better image registration. However, there are deformable image fusion protocols that allow reasonably good fusion (to selected regions) even with different positioning. For SABR, the recommended CT slice thickness for simulation is ~1.25 mm at the level of the targets, and 2.5 mm remaining of the scan, though individual practices vary.

Respiratory correlated CT scan (4-dimensional CT or 4DCT) is the recommended CT for SABR planning. Respiratory correlated scans are acquired during several respiratory cycles, in a manner that is described as ‘oversampled.’ Individual CT images are placed into discrete groups (generally 1 of 10) that correspond to a position within the respiratory cycle. This process will allow determination of the respiratory motion of the target and normal tissues; often a reconstructed video of the motion can be displayed showing this movement. If 4DCT is not available, a slow acquisition CT, CT at extremes of respiration, or even fluoroscopy can be used to determine the extent of the respiratory motion of the target. In patients with tumors in the lower lung lobes or upper abdomen, as well as in case of large tumor motion, breathhold CT scans can be recommended if patient is compliant and able to hold his/her breath for at least 20 seconds (more details below). The advantages and disadvantages of each imaging modality are detailed in the Table 4.

Tumors in the liver, especially metastatic, can be difficult to differentiate from the normal liver parenchyma. Therefore, small fiducial markers can be inserted near the tumor, for easier identification of the target on the CT simulation and CBCT. However, insertion of fiducial markers is an invasive procedure, requires day admission and rarely can be associated with complications (e.g., hemorrhage, hematoma, misplacement, migration, infection, etc.) (26-28).

Respiratory motion and its management

Respiratory motion is an important source of uncertainty in radiotherapy. It is patient-specific. Individual respiratory characteristics can vary in amplitude, period and regularity during and between SABR fractions (intra-fraction, inter-fraction). In addition, it was shown that over the course of treatment, tumors may change in size, shape and mobility. AAPM TG 76 (29) and 101 (23) recommend assessment of respiratory motion in all patients treated with SABR, while the respiratory management should be individualized. Respiratory management is recommended for all tumors moving more than 5mm in any direction. Dosimetric studies have shown that for tumor motion...
>5 mm, the interplay effect can result in underdosing of the PTV when IMRT techniques are used (30). This interplay effect is less significant when 3D CRT technique is used (same “intensity” of the beam). In our practice, respiratory management is recommended for all tumors moving more than 5 mm in any direction, when IMRT or rotational techniques are used.

Several types of management of respiratory motion have been described in the literature. They can be grouped in two main categories:

- **Passive management** (motion encompassing techniques): takes into account the total range of motion and requires knowledge of the motion extent. 4DCT (discussed above) is typically used to determine the magnitude of motion. If one were to treat a target that encompassed every position within the 4DCT scan, often the target is quite large (especially for patients with tumors in the lower lobes of the lung, liver, etc.), and can result in unwanted radiation of the neighboring normal structures.

- **Active management**: involves either limitation of the respiratory motion (breathhold techniques, abdominal compression) or monitoring the target or patient during treatment and adjusting the treatment. This can be accomplished with respiratory gating (discussed more below), in which the treatment is delivered only when the patient’s breathing is within certain phases of the respiratory cycle (usually within a relaxed breathing window) or tracking, in which the treatment machine adjusts the treatment based on the patient position.

Patients can be monitored during treatment with either an external or an internal marker of motion, or the imaging of the targeted tumor. Different correlations between external markers and internal tumor motion are reported in the literature (31-33). While active management usually results in smaller target volumes, and therefore lesser irradiation of neighboring normal structures, it is also associated with increased treatment time, therefore comfort and optimization of the patient before the treatment is mandatory. For example, patients with arthritis might require antalgic before treatment in order to be able to maintain the required treatment position; some patients might require oxygen during the treatment, etc.

### Determination of required respiratory management

1. **For targets moving less than 5 mm in any direction**—free breathing non-gated treatment can be considered. This is the most widely used technique and the easiest to implement.
2. **For targets with motion over 5 mm in any direction** the following can be implemented:
   - Respiratory gating, which requires a regular respiratory pattern, minimizes the effect of respiratory motion, by limiting the delivery of the treatment beam during specific portions (“gate”) of the respiratory cycle. Gating can reduce the volume of the neighboring normal tissue receiving unnecessary irradiation. Notably, it increases treatment time by a factor of ~3. If

<table>
<thead>
<tr>
<th>Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow-CT</td>
<td>Captures the entire range of tumor motion</td>
<td>Motion artefacts determine blurring of the images and loss of resolution; these can result in errors in delineation</td>
</tr>
<tr>
<td>CT at extreme phases of respiratory cycle</td>
<td>Theoretically captures the entire range of motion; lower workload</td>
<td>Unreliable for small tumors with wide range of motion</td>
</tr>
<tr>
<td>4DCT</td>
<td>Gold standard; capture respiratory motion over few respiratory cycles; information about the shape and mobility tumor is acquired concurrently</td>
<td>Does not take into account the daily variations in breathing pattern; requires regular breathing pattern or ability of the patient to be coached</td>
</tr>
<tr>
<td>Breath-hold CT</td>
<td>Results in the smallest GTV; if DIBH scan: lung protection</td>
<td>Highly dependent on patient compliance</td>
</tr>
</tbody>
</table>

GTV, gross tumor volume.
the respiratory gate is too narrow (i.e., treatment only within a narrow range of the respiratory cycle), then it becomes impractical, and another method should be used.

- Breathhold is a variation of gated treatment, with the treatment being delivered only when the patient is holding their breath either in deep inspiration, deep expiration, or relaxed ‘end expiration’; the latter is reported (34,35) as the most reproducible, though the choice of breathhold technique depends on patient compliance as well as how the normal tissues move relative to the target (e.g., one approach may better move the heart or liver away from a target). It is highly dependent on patient compliance and ability (i.e., their baseline respiratory function). Breathhold allows significant reduction of the set-up uncertainty, which reduces unnecessary irradiation of normal tissues (36). However, patients must be able to hold their breath for at least 15–20 seconds. It requires imaging-based treatment verification (i.e., fluoroscopy during breathhold, or surface imaging) to assure that the patient does not move or breath during treatment.

- If a patient is unable to comply with breath-hold, and exhibits an irregular respiratory cycle pattern, monophasic (patient instructed when to inhale and exhales at own pace) or biphasic (patient instructed when to inhale and exhale) coaching of the patient might be required. This is highly dependent on the ability of the patient to follow commands, and patient compliance. Coaching allows regular breathing, therefore possibility to gate, however the amplitude of motion increases, and quality of the acquired imaging is decreased (more motion artefacts).

- For patients with irregular breathing, unable to breathhold or follow commands, a 3D-SBRT free breathing approach should be employed.

In addition, for tumors situated near sensitive critical structures, the motion of the nearby organs at risk should be analyzed and considered. For tumors in the upper abdomen, in addition to the respiratory motion, other factors to be considered are stomach fullness and peristalsis. For tumors situated in the proximity of the stomach, treatment with empty stomach is recommended.

### Treatment planning

For patients undergoing radiotherapy, definition of the target and normal tissues [also called organs at risk (OAR)] is an essential part of the entire treatment process. Guidelines for the definition of the target volumes and OARs are currently available (23,29). The gross tumor volume (GTV) is defined by the Radiation Oncologist using anatomical and/or metabolic imaging (CT, PET, MRI). For SABR, it is customary not to define a clinical target volume (CTV), which considers the microscopic extension of the tumor. The internal target volume (ITV) takes into account the respiratory motion of the target, while the planning target volume (PTV) is defined to account for setup error. Figure 2 presents an example of target definition for SABR. The OAR is often defined according to available contouring atlases (37).

In order to maximize the dose received by the target and minimize the exposure of the OARs the delivered dose must be geometrically spread, by using multiple radiation beams, as well as conformal radiation techniques: 3D-conformal RT, fixed gantry intensity modulated radiotherapy (IMRT) or rotational techniques [tomotherapy, volumetric modulated arc therapy (VMAT)] (Figure 3).

There is significant variability, depending on diagnosis and individual institutional policies, in the prescribed
dose and fractionation, as well as in the acceptable OAR dosimetric constraints used (18,38-46). The choice of prescribed dose fractionation is driven mainly by the position of the tumor relative to critical organs nearby, with steep dose gradients required. Documentation of the dose received, normal tissue dose exposure, and technique utilized (including type of respiratory management) are essential, especially if re-irradiation will potentially be necessary, which is a common scenario for patients with cancer, particularly those with oligometastatic disease (47,48). Several review articles have summarized published literature in an attempt to better define normal tissue complication probabilities (NTCP) and acceptable normal tissue dose constraints after SBRT (21,23,40,49,50). This remains a complicated area of study. The AAPM TG 101 report (23) provides recommended dose-volume constraints for normal tissues, many of which are incorporated into ongoing cooperative group randomized trials. We recommend radiation oncologists and physicists adhere to the published guidelines from AAPM TG101 and the UK Consortium (51). Future research efforts should be directed towards optimizing treatment parameters, such as fractional dose and total dose, as well as specific normal tissue dose-volume constraints.

The plan is reviewed by the Radiation Oncologist, together with the Physicists and/or Dosimetrist to ensure that all requirements for target and OARs are met. In patients with multiple targets treated concurrently, care should be taken when assessing the treatment plan: dose conformity should be assessed for the individual targets, however the OAR should be evaluated on the composite plan (plan sum), to assess the contribution of each plan to each OAR.

Following acceptance of the plan by the Radiation Oncologist, a rigorous quality assurance process is performed to verify the accuracy of the treatment plan delivery. This patient-specific verification of the treatment plan can be performed using several different evaluation techniques and will depend on which treatment technique has been selected 3D-CRT, IMRT or VMAT. The AAPM TG 218 report (52) defines the methodology and tolerances required for a comprehensive and consistent pre-treatment verification programme.

**Treatment verification**

Verification of the patient positioning and target location before the treatment beam is turned on is an essential part of any radiotherapy treatment. Traditionally, MV or kV 2-dimensional images were used to verify the conventional treatments. However, with the complex treatments such as SABR, image guidance involves more sophisticated imaging modalities, especially when uncertainties related with respiratory motion are taken into account (53,54). These include:

![Figure 3](image-url) The radiation dose should be geometrically spread in order to maximize the dose received by the target and minimize the exposure of the OARs. This is achieved by using multiple beams or arcs (rotational techniques). IMRT vs. 3D: achieves better conformity of dose around irregular targets, gives better ability to control/constrain dose to OARs, but it susceptible to changes in delivered dose due to motion; RapidArc: allows faster treatment-reduced intrafraction motion, lower total MU than IMRT planning. OAR, organs at risk; IMRT, intensity modulated radiotherapy.
X-ray imaging using MV or kV photons.

3D and 4D imaging (cone beam CT-CBCT).

Newer technologies including imaging and monitoring of electromagnetic transponders (55-57) or small fiducial markers inserted near the tumor and visible on X-rays or CBCT (58-62).

Lately surface guidance is used for verification and monitoring of the patient set-up (63,64).

The next paragraphs will focus on the most widely used methods of treatment verification.

While kV imaging can be used for rapid verification of the isocenter, or alignment of bony anatomy (if obtained orthogonally—meaning 90 degree separation) the verification of the target and OARs positioning often requires volumetric images (65-68) (such as cone beam CT or CBCT). CBCT uses an imaging source and array of detectors (incorporated onto the linear accelerator) that rotate (generally 180 degrees) around a patient to generate planar imaging; CBCT is the most readily available imaging modality for online image guidance. Standard CBCTs are 3D imaging modalities, often acquired over few respiratory cycles. Therefore, caution should be used in interpretation of the data, especially when 4DCT was used to define the target. The target image might be blurred, as the CBCT will “record” the target position over few respiratory cycles (69-70).

Figure 4 presents an example of the use of CBCT for treatment verification.

Some newer linear accelerators are equipped with respiratory correlated CBCT (4DCBCT) which could be then compared with the 4DCT simulation image set. The image acquisition time can be longer (71), which can be an issue especially for unfit patients. However, 4DCBCT are especially useful for small tumors with large motion, or for tumors situated near the diaphragm (70,72,73).

The online image verification is used to insure that the target is covered within the predefined PTV, and that the organs at risk are outside predefined critical doses for a specific outcome (see Figure 5).

Another online imaging modality that can be used is fluoroscopy. This imaging modality should be used when gating is used for respiratory management, to verify that the tumor stays within the predefined gate. It is especially
important for small tumors with significant motion, which can be underestimated by CBCT (74, 75). The drawback of fluoroscopy is that it is a 2D imaging modality, however, used in conjunction with CBCT it is a very quick and elegant modality to verify gated treatments. In addition, it is a useful tool that can identify if there are any phase-delays between the surrogate and the tumor, which cannot be otherwise seen.

Regardless of the imaging modality used, the verification has to be repeated if the patient moves or if there are significant changes of the respiratory pattern.

A multidisciplinary team composed of Radiation Oncologist, Physicist and Radiation Therapists should be present at the time of treatment verification. Once the team is satisfied that all parameters of the treatment correspond to what was planned, the treatment can be delivered. If the treatment delivery is long, one might consider re-imaging mid-treatment and at the end of the session, to insure that there was not intra-fraction motion of the target.

While the methods for treatment verification are improving and become more sophisticated, one should not forget that positioning verification requires additional time for the patient in treatment positions that can be uncomfortable. The verification time should be minimized to decrease the likelihood of errors induced by patient motion.

Novel technologies for SBRT

This article focused mainly on the technical aspects of the most widely available SABR technique, using modern linear accelerators (LINACs). In the early 2000s, Cyberknife® was introduced. Cyberknife is a delivery system which allows for SABR, using real time monitoring of fiducials of bony anatomy, coupled with robotically controlled tracking of the target/patient. The more recent development of the MRI-based treatment delivery systems (with cobalt 60 radioactive sources or LINAC) similarly allows for improved accuracy of patient set-up and monitoring of intra-fraction motion; the incorporation of MR imaging also allows for adaptation of the treatment to inter-fraction anatomy changes and real time adaptation of the treatment delivery. Several teams published data for lung, liver, pancreatic, spinal tumors (76-78). However, this technique is unfortunately not widely available.

Furthermore, recently a new concept is developing namely biology guided radiotherapy. In 2018 (79), at the ASTRO meeting, a PET-integrated linac was presented

Use of a small amount of a radioactive tracer (most commonly FDG), signals the tumor location and highlights the differences between healthy cells and cancer cells. By allowing real-time identification of these emissions, this new LINAC would allow real time tracking of the tumor and therefore a new way to manage the respiratory motion without additional margins. Theoretically, this will result in minimisation of the exposure of the normal tissues to radiation, improved toxicity profile, better quality of life of these patients. This new machine is not yet in use in clinical practice.

Conclusions

SABR is a highly efficacious treatment, associated with high local control, minimal toxicity and minimal impact on the quality of life of the patients. However, SABR requires advanced technology and accuracy at all steps involved, from simulation to planning and treatment delivery. Achieving high accuracy can be challenging especially in patients with significant comorbidities, especially if long treatment times are required. All efforts should be made to minimize the treatment times, and improve the comfort of the patients.

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