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Scientific Article

Practical Considerations for the Implementation of a Stereotactic Body Radiation Therapy Program for Oligo-Metastases

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Abstract

Purpose: With multiple phase 2 trials supporting the use of stereotactic body radiation therapy (SBRT) in oligo-metastatic disease, we evaluated practices that could inform effective implementation of an oligo-metastasis SBRT program.

Methods and Materials: Using a context-focused realist methodology, an advisory committee of interprofessional clinicians met over a series of semistructured teleconference meetings to identify challenges in implementing an oligo-metastasis SBRT program. Consideration was given to 2 models of care: a subspecialist anatomic expertise model versus a single-practitioner "quarterback" model.

Results: The advisory committee structured recommendations within a context-mechanism-outcome framework. In summary, the committee recommends that during patient workup, a single practitioner arranges the minimum number of necessary tests, with case presentation at an appropriate multidisciplinary tumor board, including careful review of all previous treatments, and enrollment on clinical trials when possible. At simulation, common patient positions and immobilization on a single simulation scan for multiple sites is recommended. During radiation planning, dose-fractionation regimens should safely facilitate cumulative dose calculations, a single isocenter should be considered for multiple close targets to reduce treatment time, and adherence to strict quality assurance protocols is strongly recommended. Treatment duration should be minimized by treating multiple sites on the same day or choosing shorter dose fractionations. Team communication, thorough documentation, and standardized nomenclature can reduce system errors. Follow-up should aim to minimize redundant clinical appointments and imaging scans. Expert radiology review may be required to interpret post-SBRT imaging.

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Conclusions: These guidelines inform best clinical practices for implementing an oligo-metastasis SBRT program. Iterations using a realist approach may further expand on local contexts.

Introduction

The oligo-metastatic state hypothesizes that surgical or ablative treatment of a limited metastatic burden may lead to prolonged survival or even cure.[1] With multiple studies showing that patients with oligo-metastatic disease frequently exist, it is an emerging paradigm that has entered clinical practice.[2,3]

In fact, recent studies have shown benefit with this approach in delaying potentially toxic systemic therapy, increasing progression-free survival, and possibly even overall survival.[4-8] The Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET) phase 2 randomized controlled trial of patients with 1 to 5 oligo-metastases of any histology, compared standard of care palliative treatments with or without stereotactic body radiation therapy (SBRT) to all metastases. The study met its primary endpoint showing an increase in median overall survival from 28 to 41 months with ablative treatment ($P = .09$).[8]

Most studies have restricted their definition of the oligo-metastatic state to 1 to 3 or 1 to 5 metastases, but the maximum number for ablative therapy which would yield a clinical benefit has yet to be determined.[9] SABR-COMET-10 is a recently opened follow-up phase 3 trial that aims to assess whether there is a survival benefit to treating 4 to 10 oligo-metastatic lesions.[10] This trial may add to the literature base underpinning ablative treatment in the oligo-metastatic state, which continues to evolve. The consensus recommendations from the European Organisation for Research and Treatment of Cancer and the European Society for Radiotherapy and Oncology have defined an oligo-metastatic classification system with a decision tree encompassing 8 branches and 9 distinct oligo-metastatic states.[11] In addition, a recent review identified 64 active clinical trials assessing SBRT in oligo-metastatic disease at the time of the study period.[12]

Prior data have indicated a rapid increase in the use of SBRT for oligo-metastatic disease, and the trials mentioned previously may lead to further increases in utilization and development of new oligo-metastasis SBRT programs. However, implementing and operating an oligo-metastasis program is a complex undertaking with multiple clinical and logistical issues to consider. These can largely be attributable to the simultaneous treatment of multiple anatomic sites and the potential involvement of multiple practitioners, with limited guiding literature. The aim of this study was to identify issues that could affect implementation of an oligo-metastasis SBRT program, analyze the complexities of implementation using a realist framework, and evaluate current practices to inform guidelines for implementation of an oligo-metastasis SBRT program.

Methods

Realist evaluation

We used a realist approach to evaluate the implementation of oligo-metastasis SBRT programs in the setting of diverse and complex health care systems. Realist evaluation is a context-focused evaluative methodology that can guide the adoption of interventions in complex environments and help inform best practice.[13,14] It examines how specific processes (mechanisms) are deployed in specific circumstances (contexts) to generate real-time results (outcomes).[15] We anticipate the operational and methodological recommendations described herein may provide a guide for the implementation of an oligo-metastasis program while recognizing the diversity of local contexts.

Data collection and analysis

Between November 2019 and February 2020, an advisory committee met over 3 semistructured teleconference meetings to identify and discuss challenges that could arise when developing an oligo-metastasis SBRT program. The advisory committee consisted of interprofessional clinicians (8 radiation oncologists, 1 physicist, and 1 radiation therapist) and a health services researcher. Practitioners had varying anatomic expertise (such as lung, spine, or gastrointestinal cancers) and worked in 4 different cancer centers across North America, including both community and academic centers, with experience in delivering multisite SBRT, and with varying infrastructure, technology, and patient demographics.

All discussion items reaching consensus were aggregated to inform our program theory.

Realist evaluations begin with a program theory that specifies the ideas about how a program causes the intended or observed outcomes.[16] In the case of

implementing a new oligo-metastasis SBRT program, the authors theorized which variables could contribute to operational success. Once the program theory was developed, discussion on each of these variables ensued and recommendations were developed. The recommendations were refined and distributed back to the panel for review and feedback before completion.

Variables

Context-mechanism-outcome variables were determined through discussion and consensus a priori. Linkages were made between context, mechanism, and outcome variables to provide a framework for data interpretation, where each mechanism was aligned to specific contexts and specific outcomes. These are summarized in Figure 1.

Context

We defined patient, provider, and system context variables under 2 general models of care:

1. Anatomic expertise model: An anatomic site-based approach with a team of subspecialized radiation oncologists each involved in the consultation, planning, treatment, and follow-up of site-specific metastases.
2. "Quarterback' model: A single treating radiation oncologist coordinates treatment to all sites, using other consultants as needed, but remaining the most responsible physician throughout all treatments.

Mechanism

Mechanism variables were identified as sequential phases of the treatment pathway: initial consultation and workup, simulation, radiation planning, treatment delivery, and follow-up.

Outcome

Outcome variables were identified as performance indicators of a successful oligo-metastasis program: clinical efficacy and efficiency, technical accuracy and precision, safe delivery of treatment, and patient quality of life.

Results and Discussion

Summary recommendations are shown in Table 1 based on the context-mechanism-outcome structure. We strongly recommend all patients be treated within a clinical trial where possible, given that phase 3 trials supporting this approach are still needed. Although there is likely sufficient evidence to suggest that a subset of patients would benefit from an oligometastatic approach, we would still recommend trial enrollment to contribute to toxicity and outcome data.

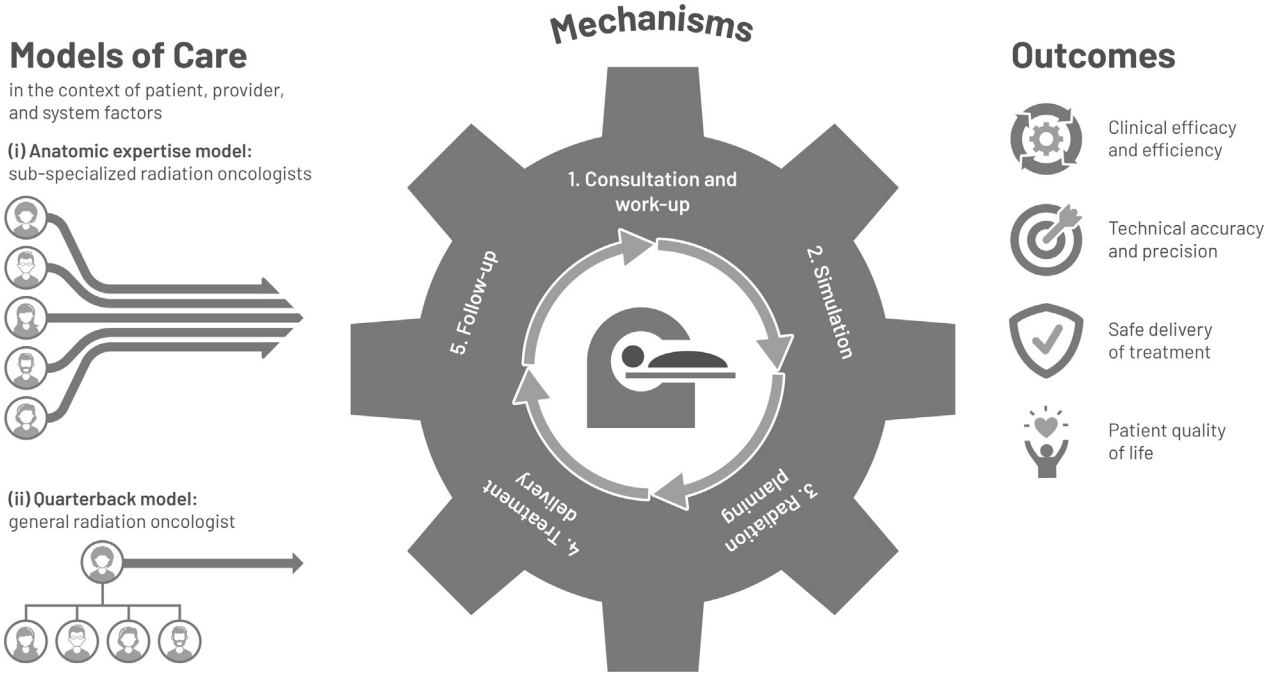

Figure 1 Program theory of operational factors in an oligo-metastasis stereotactic body radiation therapy program. A realist approach was used to evaluate the implementation of oligo-metastasis stereotactic body radiation therapy programs in the setting of diverse and complex health care systems.

Table 1 Summary of recommendations

Context	Mechanism	Outcomes
Anatomic expertise versus quarterback model: Patient • Performance status, mobility • Proximity, personal finances Provider • Oncologist subsite expertise • Departmental workflow (eg, planning team organization, QA) • Technology (eg, immobilization, treatment machine, image guidance) System • Cancer center size • Community versus academic center • Expertise of radiology department • Radiology/interventional capacity (eg, imaging, biopsy, fiducials)	**Consultation and workup** • Single provider arranges staging with minimum necessary tests (eg, imaging, biopsies) • Multidisciplinary tumor board review • Careful attention to previous treatments (eg, including radioisotopes and systemic therapy) • Treat on clinical trial when possible **Simulation** • Scan multiple sites at same session/d • Use minimum effective immobilization when safe (eg, common patient positions/ immobilization for multiple sites) • Consider single primary data set for multiple sites if overlapping dose (eg, lower lung and adrenal metastasis) **Radiation planning** • Attention to previous and current overlapping dose, including anatomic deformation of previous dose • Use single isocenter for multiple close targets to reduce treatment time • Careful attention to image registration with possible anatomic expert consultation (eg, liver, spine) • Select dose-fractionation that safely facilitates cumulative doses, using same fraction number for multiple sites where possible • Adherence to strict QA protocols subject to ongoing quality improvement **Treatment delivery** • Minimize fraction number (eg, single fraction for lung), treat multiple sites on same day or interdigitate to reduce overall/daily treatment time • Minimize system errors with team communication, thorough documentation, and standardized nomenclature **Follow-up** • Avoid unnecessary visits (multiple practitioners) and imaging scans • Expert radiology review for suspicious post-SBRT findings	Clinical efficacy and efficiency • Improved LC, PFS, OS • Reduced time from referral to RT completion Technical accuracy and precision • Target receiving planned dose Safe delivery of treatment • Minimizing errors in delivery of planned dose • Minimizing RT-related toxicity Quality of life • Consistency of oncologist • Minimizing immobilization and duration of treatment • Avoiding unnecessary follow-up • Reducing financial toxicity

Abbreviations: LC = local control; OS = overall survival; PFS = progression-free survival; QA = quality assurance; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Initial consultation and workup

Patient factors and tumor characteristics

Patient factors and tumor characteristics will vary and multidisciplinary discussion of individual cases is recommended. General factors that are considered when assessing a patient for an oligo-metastatic approach include long life expectancy, good performance status, controlled primary tumor, long disease-free interval after initial treatment for metachronous disease, and limited metastatic burden.

Multidisciplinary discussions may be structured in different ways, but options include review based on the primary tumor site (eg, thoracic cancers), a general oligo-metastasis tumor board, and site-specific oligo-metastasis

Table 2 Pre-enrollment imaging and follow-up schedules from selected oligo-metastases clinical trials

Study	Pre-enrollment	Follow-up	
	Imaging	History and physical (± laboratory tests)	Imaging
SABR-COMET[8]	Within 12 weeks: MR/CT brain, CT CAP with bone scan Alternative: PET-CT MR spine if spine mets	Every 3 mo until 24 mo, then every 6 mo until 60 mo	At 3 and 6 mo, then every 6 mo: CT HCAP and bone scan
SABR-COMET-10[10]	Within 12 weeks: PET-CT Alternative: CT NCAP with bone scan, MR/CT brain (if propensity for brain mets) MR spine if spine mets Prostate primary: PSMA- or choline PET-CT recommended	Every 3 mo until 24 mo, then every 6 mo until 60 mo	As per history and physical: CT CAP, bone scan (can omit if no bone mets at presentation), and MR/CT brain (can omit if low propensity histology) PET-CT option if used for staging
NRG LU-002[17]	Within 30 days: CT chest or PET-CT	As above, but annual follow-up after 60 mo	As per history and physical. CT chest only unless abdominal/pelvic mets
NRG BR-002[18]	Within 30 days: PET-CT or CT CAP and bone scan	Every 3 mo until 24 mo, then annual; include AST/ALT if liver SBRT	As per history and physical PET-CT strongly preferred Same imaging that originally detected metastases strongly preferred MR liver/spine if liver/spine mets
CORE[19]	Not specified	Every 3 mo until 24 mo, then every 6 mo until 60 mo; including tumor markers where applicable	Breast: CT every 3 mo until 24 mo, then every 6 mo until 60 mo NSCLC: CT every 3 mo until 24 mo, then every 6 mo until 36 mo, then yearly until 60 mo Prostate: CT at 6/12/24 mo with imaging triggered by appropriate PSA rises
STOMP[7]	MR prostate/bed ± biopsy 18F or 11C choline PET-CT MR spine/pelvis/whole body optional	Every 3 mo; including PSA	PET-CT only at PSA or symptomatic progression
Gomez et al (2019)[6]	After 1st line systemic (no timeline): PET-CT or CT CAP, MR/CT brain. Bone scan/pleural fluid aspiration optional	Every 8 weeks until 12 mo, then less frequently afterward	Every 8 weeks: PET-CT or CT chest, MR/CT brain (if brain mets)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; HNCAP = head, neck, chest, abdomen, and pelvis; MR = magnetic resonance; NSCLC = non-small cell lung cancer; PET-CT = positron-emission tomography-computed tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; mets = metastases; SBRT = stereotactic body radiation therapy.

tumor boards (eg, lung metastases-specific). An oligo-metastasis tumor board may allow time for a more thorough review and structured documentation on the planned management of each lesion, particularly when a hybrid approach with multiple modalities is taken. In these cases, a dedicated coordinator for these tumor boards may be instrumental in organizing complex treatment plans.

Workup and staging

Staging investigations should, at a minimum, include recent cross-sectional imaging, whether by a CT chest, abdomen, and pelvis scan or positron emission tomography (PET)–CT scan. Recommended imaging (with timelines) from selected clinical trials are shown in Table 2.[6-8,10,17-19] Other radiologic investigations, such as neuro-axis imaging or bone scan, should be based on the primary tumor type, location of metastases, and primary site expertise (eg, prostate-specific membrane antigen scan). Although the oligometastatic state is currently radiologically defined, elevated tumor markers should raise suspicion of a larger burden of disease and possibly prompt further investigation.[11] In an anatomic expertise model, multiple approaches to staging may be taken, potentially delaying treatment, and we would recommend a single practitioner streamline the process by arranging for the minimum number of tests that provides the necessary clinical information.

The need for biopsy confirmation should be carefully considered. The level of evidence required to treat a metastasis likely differs by jurisdiction, but the increasing numbers of metastases being treated emphasizes the potential for unnecessary radiation-related toxicity in treating a benign lesion. At the same time, this needs to be balanced against the health system implications of increased numbers of biopsies, and the risks of introducing a procedure that may cause delays in treatment initiation owing to either booking delays or related complications. From a molecular standpoint, an updated biopsy may also provide clinical information that may guide modifications in systemic therapy (eg, receptor status changes in breast cancer). Consideration should be given to noninvasive liquid biopsy on a clinical trial, if available, as current studies are assessing its utility in predicting the oligometastatic state, measuring response to treatment, and detecting progression.[20]

Determining treatment feasibility

There are a number of points to consider when determining treatment feasibility. In terms of minimum size, treating a smaller lesion needs to be weighed against the likelihood of treating a benign lesion and the ability to visualize it on cone beam CT (CBCT, with the potential for a targeting miss). Large tumors have often been excluded from clinical trials (eg, RTOG 0236[21]) owing to a theoretical decrease in local control and increased toxicity risk, but location needs to be considered (eg, center of the lung away from normal tissues). The distribution of metastases eligible for an oligometastatic approach is also unknown; for example, whether it is favorable to treat 5 metastases in a single organ versus 2 in 2 organs. There is evidence in the literature that metastases to specific organs are more prognostically favorable (eg, even left versus right liver are suggested to be prognostically different).[22,23] An upper limit for the oligometastatic state is not yet defined, and even if it were technically feasible to treat all lesions, we would advise caution, as there is a point of futility and quality-of-life effect that has only begun to be explored in the literature.[24]

Finally, close attention should be paid to previous treatments, including external beam radiation therapy (including low dose palliative treatments), brachytherapy, radioisotopes, and systemic therapy (eg, treating a central lung lesion in someone who has previously received Bevacizumab may increase the toxicity risk[25]). Although it will not always be possible to accurately account for these previous treatments, documentation is important, as they may contribute to unintended toxicities as the oligometastasis paradigm evolves. Maintaining easily accessible radiation treatment plans and 3-dimensional dose distributions will facilitate assessment of treatment overlap and potentially enable the evaluation of cumulative dose across multiple treatments.

Simulation

Multiple strategies exist for motion-management (eg, respiratory). The simplest are motion-encompassing techniques ("ITV method"), such as 4-dimensional CT, slow CT, or inhale and exhale breath hold. If target motion is relatively small, these techniques can be pragmatic in minimizing total treatment time and physical demand on patients, particularly if they are frail with multiple targets. Use of an abdominal compression device may further limit respiratory excursion for some targets by forcing shallowing breathing but is not tolerated by all patients. Both respiratory gating and active breathing control (ABC) are methods that may significantly reduce treatment volumes by either limiting radiation delivery to a portion of the patient's breathing cycle or facilitating a reproducible breath hold with a digital spirometer and balloon valve. Both methods depend on the patient maintaining a stable and reproducible breathing pattern for a minimum period of time, which is not always achievable (eg, elderly, frail patients), as well as monitoring respiratory motion using an external signal (eg, infrared reflective marker) or internal markers (eg, fiducials, dome of the diaphragm). Real-time tumor tracking, such as the robot-based CyberKnife (Accuray Inc, Sunnyvale, CA) or gimbal-based Vero systems (BrainLAB AG, Feldkirchen, Germany), generally does not have strict breathing requirements and can further minimize treatment volumes. These technologies, however, require fiducial placement. Although fiducial markers are instrumental in visualization and optimal image registration for specific tumors at CBCT (eg, pancreatic, liver), placement procedures can delay treatment start owing to scheduling and are not always feasible (eg, low platelet counts due to systemic therapy

or poor general condition). Close coordination with interventional radiology is also essential.

There will typically be multiple simulation options when treating a patient with multiple targets. Minimizing the number of simulation scans is recommended, especially if there is anatomic overlap. This may require coordination between practitioners in an anatomic expertise model. We suggest having defined simulation protocols for each immobilization technique but would advise against having a rigid protocol for each anatomic site, particularly when treating multiple sites. For example, in the case of a lower lung and adrenal metastasis, a single primary data set for treatment planning and the documentation of a composite dose distribution may be desirable as there could be dose overlap. If abdominal compression were used for the lung lesion (as some cancer centers routinely do), then that may actually compress normal tissues (eg, bowel) toward the adrenal target. A different immobilization or motion management technique for the lung lesion could be beneficial in this case.

In addition to simplifying composite dosing, the added time on the treatment unit with multiple techniques needs to be considered and minimized if possible. For example, instead of using abdominal compression for a lung lesion and ABC-assisted breath-hold for a liver lesion, ABC could be used for both if the patient is able to hold his breath. Conversely, if motion of the liver target was reasonably small, using compression for both sites could be more tolerable for the patient with significantly faster treatment times. Similar efforts should be made to minimize the need to move patients between treatment units (eg, moving from one unit with ABC to another unit with BodyFIX/HexaPOD). Overall, we recommend using the minimum effective immobilization on a single treatment unit when safe.

Radiation planning

Effective and safe radiation therapy planning within the oligometastatic paradigm requires close attention to detail. Accurate image registration, previous dose (we will not be reviewing normal tissue repair given the lack of consensus for best practice), and the integration of multiple current plans are just a few examples of what needs to be carefully reviewed in a thorough quality assurance protocol.

As 4-dimensional CT images, multiphasic contrast CT images (eg, liver), and MRI images (eg, spine) will often need to be fused to a helical planning CT, an ability to assess the accuracy of the image registration will be essential for target accuracy and safety. For those centers using the quarterback model, anatomic expert consultation may be required.

In terms of previous radiation therapy treatments, simply fusing previous dose distributions based on rigid registration to account for overlap may be insufficient given the anatomic shifts that can occur (eg, radiation lung fibrosis affecting the position of the bronchus, mobile bowel). The use of deformable image registration to accumulate multiple courses of radiation treatment has the potential to provide spatially accurate assessment of overlapping dose distributions. However, routine clinical use of deformable registration requires careful commissioning and dedicated quality control processes, to both understand the limitations of the algorithms and appreciate the underlying uncertainty in the accumulated dose estimates.[26] Current software that is able to summarize previous doses on a single image set is likely most beneficial in notifying practitioners that general anatomic regions have received a meaningful dose.

Clinical trials often use varying dose-fractionations, making it difficult to integrate into clinical practice. We recommend an approach that safely facilitates cumulative doses, using the same number of fractions for multiple sites where possible given the challenges associated with combining multiple distributions that have different dose-per-fractions and assessing biologic equivalence. Minimizing the total number of fractions to reduce patient visits would also be advisable, though hypo-fractionated conventional RT remains an option in cases where it may be difficult to meet normal tissue constraints (eg, previous treatment).

Strict protocols for quality assurance (QA) of radiation plans should be followed, and the protocols themselves subject to ongoing quality improvement, as per American Society for Therapeutic Radiology and Oncology guidelines.[27] Depending on the structure of QA rounds at different centers, cases may need to be reviewed in multiple rounds (eg, lung and spine rounds) with direct consultation with anatomic experts. Attendance of QA rounds by radiation oncologists, therapists, and physicists is necessary to review treatment indications and diagnostic imaging, plan contours and dosimetry, image guidance issues, and serve as a forum for wider technical considerations, education, and research. A major benefit of an oligo-metastasis–focused QA rounds could be a more structured review of each case and establishment of a consistent group approach which would improve outcome assessment.

Multiple radiation plans will need to be integrated when treating multiple targets. This will be even more important when large overlap between treatments is expected, such as delivering noncoplanar radiation beams or treating targets with large ITVs (eg, right lower lung and liver lesions with overlapping normal liver and lung doses). This may be simplified in some cases by using a single isocenter to treat multiple targets in close proximity, which could also streamline patient setup and significantly reduce total treatment time. However, this

could also introduce challenges at planning, particularly with volumetric modulated arc therapy (VMAT), as beam delivery constraints limit the modulation required to generate conformal dose distributions around spatially distinct targets. Additionally, a single CBCT using a fixed isocenter will limit the field-of-view and extent of anatomy that can be visualized on treatment. Although combining multiple CBCT to generate a large effective field-of-view is feasible on current commercially available delivery systems, achieving a successful registration across a large region may require compromise and necessitate increased PTV margins.

Treatment delivery

Multiple radiation therapy schedules for multiple targets increase the risk of both prolonging treatment for patients, interruptions in systemic therapy, and introducing potentially dangerous system errors.

To minimize this effect, efforts should be made to minimize the total number of fractions being delivered, the total number of visits the patient is asked to attend, and the duration of each visit. Practitioners may want to consider alternative fractionations, such as single-fraction radiation therapy for lung metastases, which was shown to be both effective and safe in RTOG 0915.[28] This could be particularly beneficial for patients from out of town who often experience significant financial toxicity associated with travel and lodging during treatment. The use of a continuous delivery technique such as volumetric modulated arc therapy also has the potential to reduce total delivery time compared with conventional intensity modulated radiation therapy. Furthermore, considering the relatively large dose-per-fraction prescribed to oligometastasis, the use of flattening-filter–free modalities with high-dose-rates can significantly reduce treatment times, in particular for small target volumes that do not require a high-degree of modulation to achieve a uniform dose distribution.

The sequencing of treatments is another important consideration. Treating multiple sites on the same day or interdigitating treatments has the advantage of reducing the overall treatment time and course duration for the patient but may increase toxicity and the risk of intrafraction movement (Fig 2). It also highlights the increased risk of system error and the importance of team communication and thorough documentation, including the unequivocal identification of targets and treatment plans with an accepted nomenclature system. For example, in a patient with multiple lung metastases, it is essential to label and track each target, its corresponding dose and fractionation schedule, and how many fractions it has received (eg, if not all lesions are treated simultaneously). Treatment plans in which 2 or more lesions in close proximity are simultaneously treated with one isocenter can also increase complexity and necessitate fastidious documentation. Standardized target and treatment plan nomenclature is also integral to the accuracy and efficiency of treatment delivery and improves workflow on the treatment units. Radiation therapists, among others present during treatment, rely on this documentation to ensure that the correct lesion(s) is identified and matched during CBCT image verification. This is also important at CT simulation, for example in a patient with multiple lung lesions, to assess and record

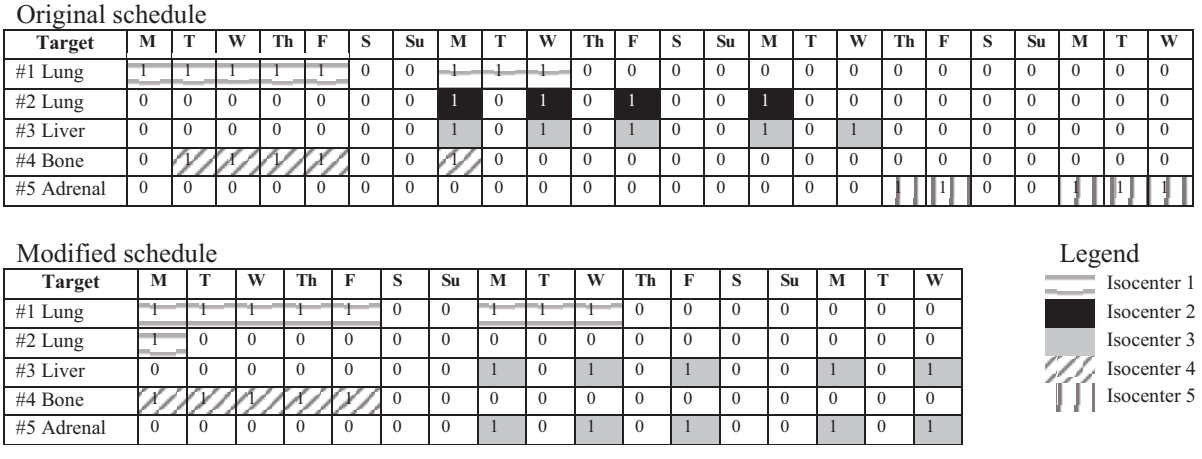

Figure 2 Suggested radiation therapy schedule modifications. Multiple targets can be treated on the same day to reduce overall treatment duration (eg, lung and bone) but careful consideration should also be given to prolonged patient set-up times as a result (eg, second Monday of original schedule). Set-up time could be significantly reduced by using shared isocenters for multiple close targets (eg, multiple lung versus liver/adrenal). Alternative dose-fractionation regimens such as single-fraction lung stereotactic body radiation therapy may also reduce treatment burden (target 2). *Abbreviation:* 0/1 = no/yes treatment of target on specific day.

the degree of respiratory motion for each target and to determine whether certain immobilization (eg, abdominal compression) or motion management techniques are warranted.

Image guidance protocols should be taken under consideration in the implementation of an SBRT program. CBCT image verification is essential for geographic localization and accuracy. Where resources are available, pretreatment CBCT matching may also be supplemented by other patient monitoring techniques such as surface-guided radiation therapy systems and intrafractional imaging (eg, triggered kV images).

Although not yet widely available, MR Linac technology has the potential to benefit patients in myriad circumstances. These hybrid machines not only have the capacity to improve pretreatment image verification by enhancing visualization of targets and critical normal structures, but also to provide continuous and real-time intrafraction monitoring without additional ionizing radiation.

The literature available on the optimal timing of SBRT with systemic therapy remains limited. Despite increasing use of immune checkpoint inhibitors (ICI), the toxicity of combined modality treatment is still largely limited to nonrandomized data. A recent review by Bang and Schoenfeld looked at nonrandomized prospective trials in the metastatic setting (radiation therapy combined with CTLA-4 or PD-1 inhibitors) and found grade 3 to 5 toxicity rates similar to what would be expected with ICI alone (14%-34% and 5%-10%, respectively), and with few serious toxicities attributed to the radiation therapy component.[29] ICI was given concurrently or within 7 days of completing radiation therapy in these trials, though many used palliative doses. There was a randomized phase 2 trial by Theelen et al in patients with metastatic non-small cell lung cancer that did not observe significantly increased grade 3 + toxicity rates when SBRT was given within 7 days before pembrolizumab.[30] Considering the prolonged half-life of ICI, SBRT delivered concurrently or shortly after administration of ICI may not significantly affect toxicity rates. Close multidisciplinary communication is necessary to implement a safe treatment schedule, in general. Table 3 summarizes recommended schedules from several notable oligo-metastasis trials for different systemic therapies.[6,8,10,17,18] Particular caution is advised in patients receiving radiosensitizers such as bevacizumab.

Post-SBRT follow-up

The focus of follow-up should be on disease control, treatment-related toxicity, and patient quality of life, with an emphasis on coordinating with other colleagues and disciplines to minimize redundant patient visits and imaging tests.

The follow-up schedules of several notable previous and current randomized trials are summarized in Table 2. These schedules are more pragmatic than evidence based as there is no level 1 evidence to provide more definitive guidance.

Anatomic expertise model

The subspecialized practitioner would possess a deeper familiarity with interpretation of laboratory tests, management of toxicities, and follow-up protocols associated with that specific site.

Knowing how to interpret response to SBRT (eg, in lung metastases) is another advantage, as assessing local recurrence often requires both a skilled radiologist and clinical input. Site-specific expertise would also inform future investigative decisions, for example in understanding the utility of a PET-CT scan after lung SBRT.

This model, however, also lends itself to logistical and quality of life issues if a patient is required to attend multiple appointments and potentially redundant imaging scans. Efforts should be made to reduce patient travel and limit financial toxicity (eg, by booking visits and imaging on the same day), and to adhere to recommendations outlined by Choosing Wisely Canada.[31]

Quarterback model

The single MRP model provides more clarity and consistency of care. The practitioner would be free to organize tests and follow-up without having to coordinate with other team members, decreasing the risk of communication errors (eg, not booking follow-up imaging). This may reduce patient anxiety. Anatomic expert opinion could also be sought within one's own departmental group on a consultation basis if needed.

Strengths and limitations

The recommendations presented in this study have not been validated as there remains limited evidence in the oligo-metastatic disease treatment pathway. The intention was to highlight practical considerations for others developing their own oligo-metastasis SBRT programs, as opposed to rigid algorithms. The realist methodology provided an effective framework to explore the factors that may contribute to effective implementation within different contexts.

Although we attempted to address the diversity within these contexts, this still represents a North American perspective. The balance between efficacy and safety may shift depending on the geographic region and circumstance, but this study provides a framework for future discussion as the oligo-metastatic disease paradigm evolves.

Table 3 Recommendations for timing of systemic therapy from selected oligo-metastases clinical trials

Study	Stop pre-SBRT			Restart post-SBRT	Notes
	Targeted molecular therapy	Cytotoxic therapy	Immuno-therapy		
SABR-COMET[8]	4 wk prior	4 wk prior	4 wk prior	2 wk post	Hormonal therapy allowed during RT
SABR-COMET 10[10]	2 wk prior	2 wk prior	2 wk prior	1 wk post	Hormonal therapy allowed during RT Radioenhancers (eg, gemcitabine) discouraged within first month
NRG LU-002[17]	Not specified	Must register within 35 d of completion of prior induction chemotherapy NOS	Not specified	2 wk post	Excluded: prior bevacizumab or other targeted therapy for NSCLC in first line setting
NRG BR-002[18]	2-3 wk prior for 2-4 wk cycles; 1 wk prior for weekly cycles Concurrent palbociclib, everolimus, trastuzumab-emantansine not permitted.	2-3 wk prior for 2-4 wk cycles; 1 wk prior for weekly cycles Concurrent cytotoxic therapy not permitted	Not specified	4 wk post	Concurrent hormone therapy, bone supportive therapy, biologics (eg, trastuzumab, pertuzumab) permitted. Experimental therapeutics require 30-d washout (eg, bevacizumab)
Gomez et al (2019)[6]	TKIs (eg, erlotinib) permitted with standard (≤3 Gy/fraction) and hypofractionation (≥3 Gy/fraction)	Not specified	Not specified	Not specified	Bevacizumab not permitted within 2 wks before SBRT

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer; RT = radiation; SBRT = stereotactic body radiation therapy; TKI = tyrosine-kinase inhibitor.

Conclusions

Using a realist approach, we identified practical considerations for the implementation of an oligo-metastasis SBRT program. Iterations of this approach could further expand on local contexts.

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