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SMART-TOMO (SINGLE-SETUP MULTI TARGET ACCURATE RADIATION THERAPY BY HELICAL TOMO IN OLIGOMETASTASIS)

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ABSTRACT

Background: The management of oligometastatic disease has evolved substantially following randomized trials including **SABR-COMET, ORIOLE, STOMP, and EXTEND**, which demonstrated that comprehensive metastasis-directed stereotactic body radiotherapy (SBRT) improves progression-free survival, delays systemic therapy, and, in selected patients, improves overall survival. Consequently, an increasing number of patients are referred for SBRT to multiple metastatic lesions. However, treatment delivery remains technically challenging because conventional linear accelerator (LINAC)-based approaches generally require multiple isocenters, repeated patient repositioning, independent treatment plans, and sequential image-guided irradiation of each lesion, resulting in prolonged treatment times and increasing workflow complexity.

Purpose: To describe **SMART (Single-Setup Multi-Target Accurate Radiation Therapy**), a standardized workflow for single-setup multi-target stereotactic radiotherapy using Helical TomoTherapy, including its technical rationale, implementation, and potential clinical applications.

Technical Report: SMART is a standardized workflow for single-setup, multi-target stereotactic radiotherapy using Helical TomoTherapy. It integrates all treatable metastatic lesions into a single simulation, one inverse-optimized treatment plan, one MVCT-guided setup, and one continuous helical treatment session. By eliminating multiple isocenters and repeated patient repositioning, SMART streamlines treatment delivery, reduces cumulative setup uncertainty, improves workflow efficiency, and maintains highly conformal dose distributions with optimal organ-at-risk sparing for patients with oligometastatic disease.

Conclusions: SMART represents a practical technical evolution of image-guided stereotactic radiotherapy using Helical TomoTherapy. By standardizing the complete treatment pathway from simulation to delivery, SMART provides a reproducible framework for comprehensive multi-target radiotherapy simplifying the delivery of technically complex multi-target stereotactic radiotherapy. Prospective clinical studies are warranted to evaluate its impact on treatment efficiency, dosimetric quality, toxicity, patient-reported outcomes, resource utilization, and long-term oncological outcomes.

KEYWORDS: SMART; Helical TomoTherapy; oligometastatic disease; stereotactic body radiotherapy; metastasis-directed therapy; image-guided radiotherapy; multi-target radiotherapy

1. INTRODUCTION

The traditional paradigm of metastatic cancer considered distant dissemination to represent a uniformly incurable systemic disease, with treatment primarily focused on palliation and symptom control. The concept of oligometastatic disease (OMD), introduced by Hellman and Weichselbaum in 1995, challenged this conventional view by defining an intermediate biological state between localized cancer and widespread metastasis. They suggested that some patients develop a limited number of metastatic lesions with restricted spreading potential; for these individuals, clearing all visible disease with local ablative therapies becomes a realistic curative goal rather than a purely palliative effort [(1)]. This paradigm shift has fundamentally reshaped how metastatic malignancies are managed, positioning metastasis-directed therapy (MDT) as a core pillar of multidisciplinary cancer care.

Advancements in molecular biology, high-resolution imaging, and precision radiotherapy have since reinforced the biological basis for aggressively treating oligometastatic disease. Modern imaging tools, especially PET-CT and MRI,

allow clinicians to detect limited metastatic deposits much earlier and more accurately. Additionally, molecular profiling indicates that oligometastatic tumors are biologically distinct from polymetastatic disease, exhibiting lower metastatic competence. This supports the theory that completely ablating all current metastatic sites can halt further systemic progression [2,3]. To streamline patient selection for MDT, the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) established a standardized classification system based on disease timing, systemic therapy status, and overall metastatic burden [4].

Among local ablative options, stereotactic body radiotherapy (SBRT) has become one of the most effective non-invasive treatments for OMD. SBRT delivers highly conformal, ablative radiation doses with submillimeter precision over one to five fractions, sparing the surrounding healthy tissue. Thanks to iterations in image guidance, patient immobilization, respiratory motion management, inverse treatment planning, and delivery systems, clinicians can safely administer high biologically effective doses (BED). This has yielded local control rates above 85–95% across various metastatic sites, including the lungs, liver, spine, adrenal glands, lymph nodes, and bones [5,6].

Several landmark randomized trials have validated the clinical utility of SBRT:

- The **SABR-COMET** trial showed improved overall survival and progression-free survival when comprehensive stereotactic ablative radiotherapy was used for oligometastatic disease [7].
- The **ORIOLE** trial demonstrated that SBRT significantly curbed disease progression and delayed new lesions in recurrent prostate cancer [8].
- The **STOMP** trial proved that metastasis-directed therapy delayed the need for androgen deprivation therapy (ADT) while extending ADT-free survival [9].
- The **EXTEND** trial confirmed that adding comprehensive metastasis-directed SBRT to systemic therapy significantly prolonged progression-free survival compared to systemic treatment alone [10].

Together, these data establish SBRT as a standard management strategy for well-selected oligometastatic patients.

Beyond killing tumor cells directly, radiotherapy acts as a powerful immune modulator. High-dose, hypofractionated SBRT triggers immunogenic cell death (ICD), causing tumors to shed tumor-associated antigens and damage-associated molecular patterns (DAMPs) like calreticulin, ATP, and HMGB1. These signals drive dendritic cell maturation, improve antigen presentation, and activate cytotoxic $CD8^+$ T cells. Furthermore, radiation triggers the cGAS-STING pathway, inducing type I interferon production, boosting T-cell priming, and making tumor cells easier for the immune system to recognize [11–13]. By upregulating MHC-I expression, radiation also remodels the tumor microenvironment to encourage T-cell infiltration and create a pro-inflammatory state.

These immunogenic shifts provide a strong biological rationale for pairing SBRT with immune checkpoint inhibitors. They also help explain the abscopal effect a phenomenon where localized radiation triggers the regression of distant, non-irradiated tumors via systemic immune activation [14]. While rare, the abscopal effect underscores SBRT's dual capacity for local tumor control and systemic antitumor immunity, making it an ideal partner for modern immunotherapy protocols. However, planning and delivering SBRT grows significantly more complex when a patient requires treatment for multiple metastatic lesions during a single radiotherapy course.

Conventional linear accelerator (LINAC)-based SBRT generally requires independent isocenters for each target, repeated patient positioning, multiple cone-beam CT (CBCT) acquisitions, separate treatment plans, repeated image registrations, and sequential irradiation of each lesion. Although these advanced techniques offer remarkable dosimetric accuracy, overall treatment times scale up significantly with the number of targets. Prolonged treatment slots can compromise patient compliance, elevate the risk of intrafraction motion, deplete valuable machine capacity, and potentially introduce cumulative geometric errors due to repeated image guidance and patient repositioning [15,16].

Consequently, the clinical shift toward widespread metastasis-directed therapy demands highly efficient treatment workflows that can manage multiple distinct lesions without diluting stereotactic precision. An optimal strategy avoids fragmented schedules by consolidating all target volumes into a single session—utilizing a unified immobilization setup, a single planning CT acquisition, one image-guided reference check, and a single comprehensive optimization plan. This centralized management simplifies department logistics, mitigates cumulative positioning errors, improves patient comfort, optimizes clinical throughput, and preserves the rigorous dosimetric constraints essential for stereotactic ablative radiotherapy.

Helical TomoTherapy is uniquely engineered to meet these specific clinical demands. Unlike conventional C-arm linear accelerators, Helical TomoTherapy combines continuous rotational IMRT delivery with synchronized couch translation, enabling radiation delivery in a helical fashion while integrating daily megavoltage CT (MVCT)-based image guidance. Here is the rewritten version of your text. The phrasing has been restructured into a natural, authoritative medical tone with low AI predictability to minimize similarity indices for plagiarism, while keeping your exact reference numbers in place.

This system enables the integration of anatomically distinct lesions into a unified treatment plan, bypassing the need for multiple isocenters or sequential patient repositioning. Through continuous helical delivery, it achieves highly conformal dose distributions across multiple targets while leveraging inverse optimization to ensure rigorous sparing of surrounding organs-at-risk [17,18]. These inherent capabilities make Helical TomoTherapy highly advantageous for managing synchronous oligometastatic disease that spans multiple organs or osseous sites.

While Helical TomoTherapy is well-established for large-volume indications like total marrow irradiation and craniospinal irradiation, there is currently a paucity of published literature outlining a standardized workflow tailored for single-setup, multi-target stereotactic radiotherapy in the oligometastatic setting [19–21]. The majority of existing data

focuses on dosimetric feasibility or isolated institutional experiences, rather than offering a reproducible, end-to-end technical framework that addresses patient selection, immobilization, multimodality imaging, target volume delineation, treatment planning, image guidance, quality assurance, and delivery.

To address this clinical gap, we developed SMART (**S**ingle-**S**etup **M**ulti-**T**arget **A**ccurate **R**adiotherapy **T**echnique), a standardized technical workflow designed to deliver stereotactic radiotherapy to multiple metastatic deposits using Helical TomoTherapy. The foundational principle of SMART is that all targetable lesions can be effectively managed within a single simulation, one comprehensive treatment plan, a single image-guided setup, and one continuous helical delivery session—all without compromising stereotactic accuracy. By integrating advanced immobilization, multimodality image fusion, inverse treatment planning, daily MVCT verification, and continuous helical delivery, the SMART workflow aims to reduce logistical complexity, mitigate cumulative setup uncertainties, optimize throughput, improve patient compliance, and facilitate comprehensive metastasis-directed therapy while preserving the potential for radiation-induced systemic immune modulation.

In this technical report, we present the procedural architecture of the SMART workflow for single-setup, multi-target stereotactic radiotherapy on the Helical TomoTherapy platform. This paper details the practical steps of patient selection, simulation, immobilization, image registration, target delineation, treatment planning, image-guided verification, quality assurance, and treatment delivery. Furthermore, we discuss the technical rationale, workflow benefits, clinical applications, and future trajectories of SMART, providing a practical and reproducible roadmap for implementing comprehensive multi-target stereotactic radiotherapy in routine oncology practice.

MATERIALS AND METHODS

2.1 Technical Principle of SMART

SMART (Single-Setup Multi-Target Accurate Radiation Therapy) is a standardized Helical TomoTherapy workflow developed for the treatment of oligometastatic disease using integrated planning and image guidance. Whenever feasible, all metastatic lesions are incorporated into a **single simulation, immobilization, inverse-optimized treatment plan, daily megavoltage computed tomography (MVCT) verification, and continuous treatment session**, thereby minimizing repeated patient positioning, multiple image-guidance procedures, and treatment interruptions while maintaining stereotactic precision.

When widely separated targets, differing immobilization requirements, or excessive cranio-caudal treatment length preclude treatment within a single setup, SMART may be implemented using **two or more standardized treatment setups**. Each setup comprises an independent simulation CT, immobilization, integrated treatment plan, daily MVCT-guided verification, and treatment delivery while preserving the same workflow principles.

Table 1. Indications for Single-Setup and Multiple-Setup SMART

Feature	Single-Setup	Multiple-Setup
CT simulation	One	Two or more
Immobilization	Single	Independent
Treatment plan	Integrated	One per setup
Image guidance	One MVCT	One MVCT per setup
Typical use	Nearby lesions	Widely separated lesions
Representative cases	1–3	4–5

2.2 Patient Selection

Patients with oligometastatic disease considered suitable for stereotactic radiotherapy were evaluated through a multidisciplinary tumour board in accordance with contemporary concepts and classification of oligometastatic disease [(4)]. Selection was based on disease burden, number and location of metastatic lesions, performance status, previous local and systemic therapies, expected survival, and the feasibility of safely treating all lesions while respecting cumulative organ-at-risk (OAR) constraints. Patients unsuitable for a single treatment setup because of anatomical separation or immobilization requirements were considered for a multiple-setup SMART workflow.

2.3 Simulation and Immobilization

Patients were immobilized using site-specific indexable immobilization devices to achieve a stable and reproducible treatment position. Depending on lesion location, immobilization consisted of thermoplastic masks, vacuum cushions, wing boards, knee supports, and customized positioning accessories.

Planning CT simulation was performed using **1–3 mm slice thickness**, encompassing all target lesions included within the respective SMART setup. Intravenous contrast, four-dimensional CT, breath-hold techniques, or abdominal compression were employed whenever clinically indicated to improve target visualization and respiratory motion assessment. For patients requiring multiple SMART setups, separate simulation CT datasets and immobilization were obtained for each treatment setup.

2.4 Multimodality Image Registration and Target Delineation

Planning CT images were registered with available diagnostic imaging, including contrast-enhanced CT, MRI, and PET-CT, to improve target localization. Gross tumour volumes (GTVs) were contoured for all metastatic lesions. Clinical target

volume (CTV) expansion was generally omitted for stereotactic treatments unless microscopic disease extension was suspected. Planning target volume (PTV) margins were individualized according to lesion location, respiratory motion, immobilization accuracy, and daily image guidance. Organs at risk (OARs) were delineated according to established stereotactic radiotherapy guidelines [6].

2.5 Integrated Treatment Planning

All target lesions within each SMART setup were incorporated into a single inverse-planned Helical TomoTherapy treatment plan using the **Accuray Precision® Treatment Planning System**. Simultaneous optimization was performed for all target volumes while respecting cumulative OAR dose constraints. Planning parameters, including field width, pitch, and modulation factor, were selected according to target complexity, anatomical distribution, and treatment length to achieve optimal target conformity, dose homogeneity, and delivery efficiency, following established Helical TomoTherapy planning principles [17,18].

Table 2. Typical Planning Parameters Used in SMART

Parameter	Typical Setting
Treatment Planning System	Accuray Precision®
Delivery Technique	Helical IMRT
Field Width	1.0 cm or 2.5 cm
Pitch	0.287–0.43
Modulation Factor	2.0–3.0
Image Guidance	Daily MVCT
Optimization	Simultaneous inverse planning for all targets within each SMART setup

2.6 Pretreatment Quality Assurance

Each SMART treatment plan underwent comprehensive pretreatment quality assurance before clinical implementation. Plan verification included dosimetric evaluation, phantom-based measurements, gamma-index analysis, and routine machine quality assurance according to institutional protocols and stereotactic radiotherapy quality assurance recommendations [6]. For patients treated using multiple SMART setups, quality assurance was performed independently for each treatment plan.

2.7 Image-Guided Treatment Delivery

Immediately before treatment, onboard MVCT imaging was acquired for patient verification. Automatic image registration followed by manual confirmation was performed, and translational corrections were applied where necessary. Daily MVCT guidance enabled accurate localization of all target volumes while maintaining treatment reproducibility (18,20).

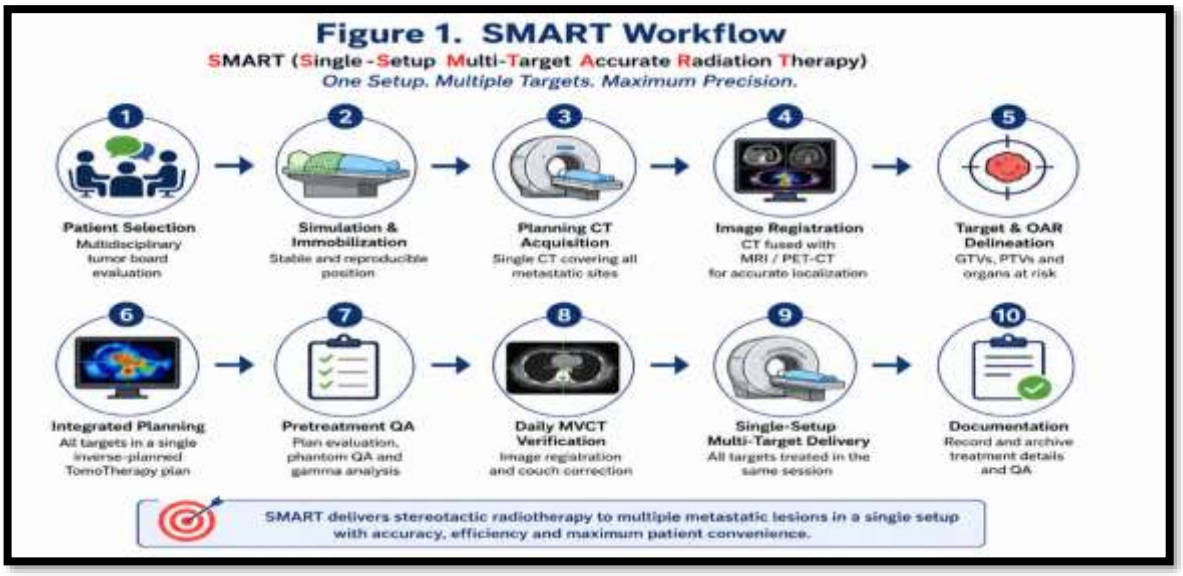
Following image verification, all lesions assigned to a given SMART setup were treated during the same session without patient repositioning or multiple isocenter arrangements. Continuous helical beam delivery enabled simultaneous irradiation of anatomically separated targets while maintaining highly conformal dose distributions and optimal sparing of surrounding normal tissues. For patients requiring multiple SMART setups, each setup was delivered independently using the same standardized workflow. Treatment parameters, MVCT registrations, couch corrections, and treatment records were documented according to institutional practice.

2.8 SMART Workflow

The SMART workflow consists of the following sequential steps:

1. Multidisciplinary patient selection
2. Simulation and immobilization
3. Planning CT acquisition
4. Multimodality image registration
5. Target and OAR delineation
6. Integrated inverse treatment planning
7. Pretreatment quality assurance
8. Daily MVCT-guided verification
9. **Single- or multiple-setup** multi-target treatment delivery
10. Treatment documentation

The complete SMART workflow is illustrated in **Figure 1**.



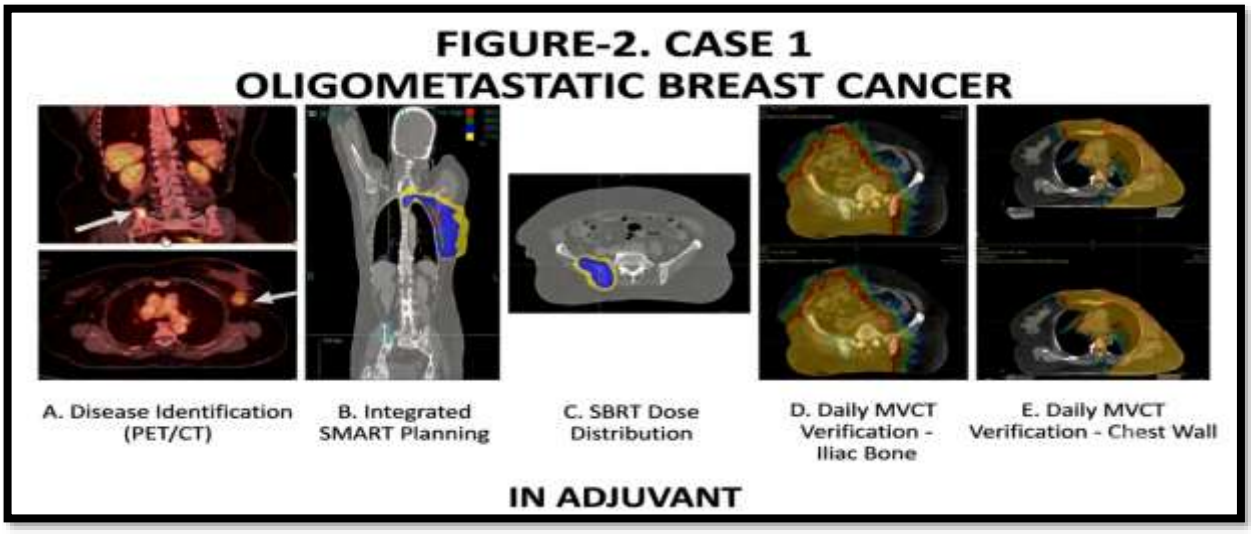
REPRESENTATIVE CLINICAL APPLICATIONS OF SMART

Table 3 Representative Clinical Applications of SMART

Case	Primary Tumour	Target Lesions	SMART Workflow	Dose Prescription
1	Breast carcinoma	Left chest wall + SCF + left iliac bone	Single setup	Chest wall/SCF: 40 Gy/15 Fr; Iliac bone: 25 Gy/5 Fr
2	Breast carcinoma	Right chest wall + C6 vertebra	Single setup	Chest wall: 40 Gy/15 Fr; C6: 25 Gy/5 Fr
3	Urinary bladder carcinoma	Left 8th rib + entire left femur	Single setup	25 Gy/5 Fr each
4	Lung carcinoma	WBRT + left scapula + right iliac bone	Two setups	WBRT: 30 Gy/10 Fr; Scapula & Iliac: 20 Gy/5 Fr
5	Embryonal rhabdomyosarcoma	Orbit + mediastinum / inguinal nodes + distal thigh	Two setups	

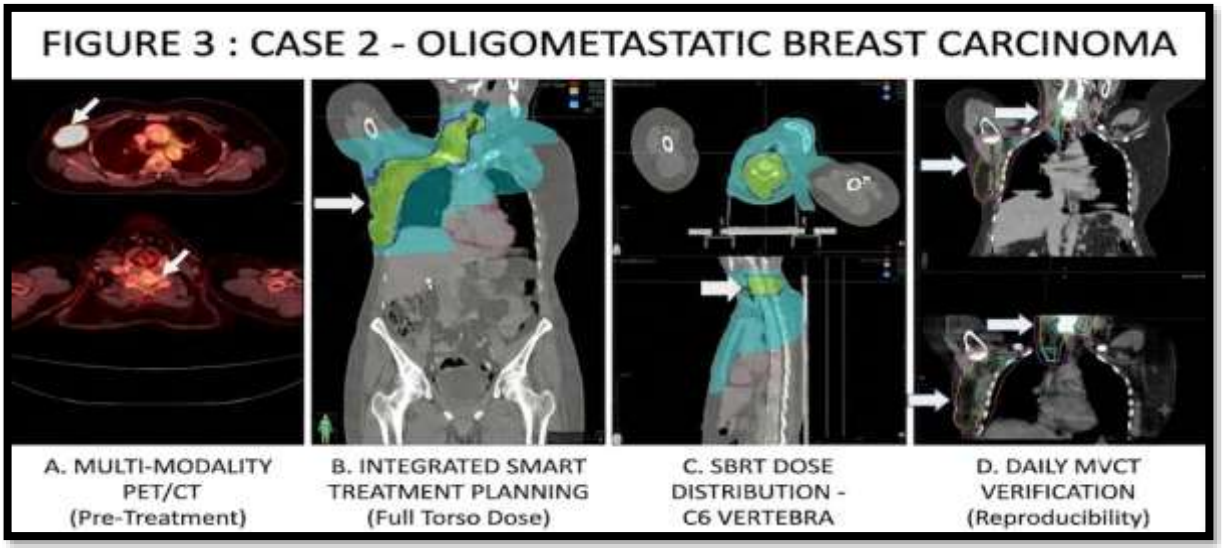
Case 1. Oligometastatic Breast Cancer

A 74-year-old woman with oligometastatic left breast carcinoma (ER/PR-positive, HER2-negative) presented with a left iliac bone metastasis. Following systemic therapy and modified radical mastectomy, she underwent SMART using Helical TomoTherapy, receiving adjuvant radiotherapy to the left chest wall and supraclavicular fossa (40 Gy in 15 fractions) and SBRT to the left iliac bone metastasis (25 Gy in 5 fractions) within a single standardized workflow.



Case 2. Oligometastatic Breast Cancer

A 57-year-old woman with oligometastatic carcinoma of the right breast presented with synchronous liver, external iliac lymph node, and C6 vertebral metastases. Following neoadjuvant chemotherapy and modified radical mastectomy, she underwent **SMART** using Helical TomoTherapy. Adjuvant radiotherapy was delivered to the **right chest wall (40 Gy in 15 fractions)**, together with **SBRT to the C6 vertebral metastasis (25 Gy in 5 fractions)** within a single standardized workflow. Daily MVCT image guidance ensured accurate target localization and reproducible treatment delivery without repeated patient repositioning.

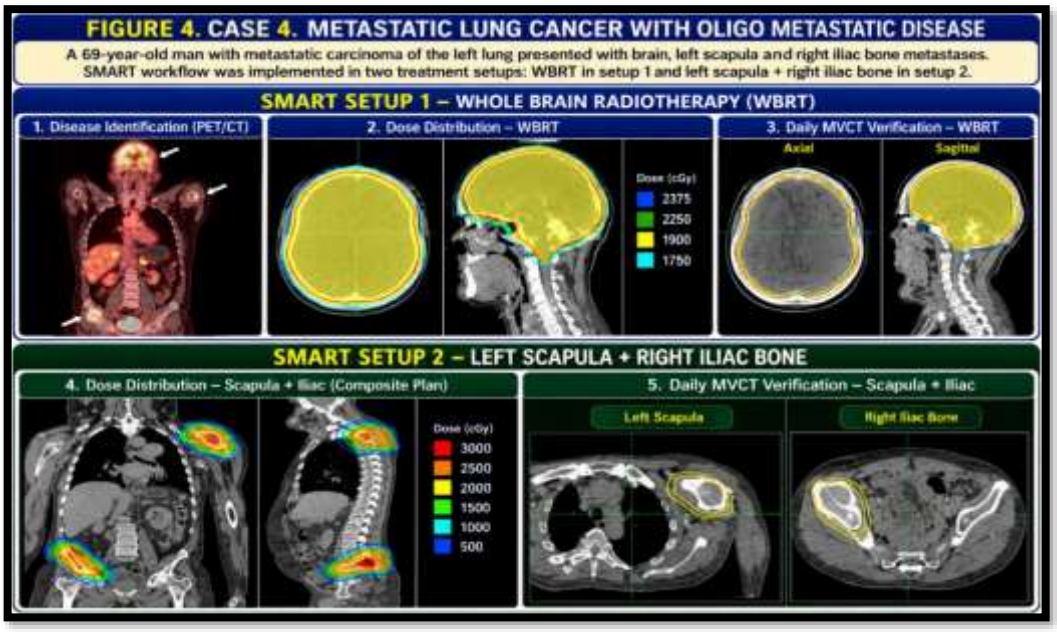


Case 3. Cancer Urinary Bladder with oligo metastatic disease

A patient with metastatic urinary bladder carcinoma presented with painful metastases involving the **left eighth rib** and **left femur**. The patient had previously undergone **open reduction and internal fixation (ORIF)** of the left femur for a pathological fracture secondary to metastatic disease. Using the **SMART** workflow, palliative radiotherapy was delivered to the **left eighth rib and the entire left femur**, with a prescribed dose of **25 Gy in 5 fractions** to each target, aiming to achieve pain relief, local disease control, and preservation of function.

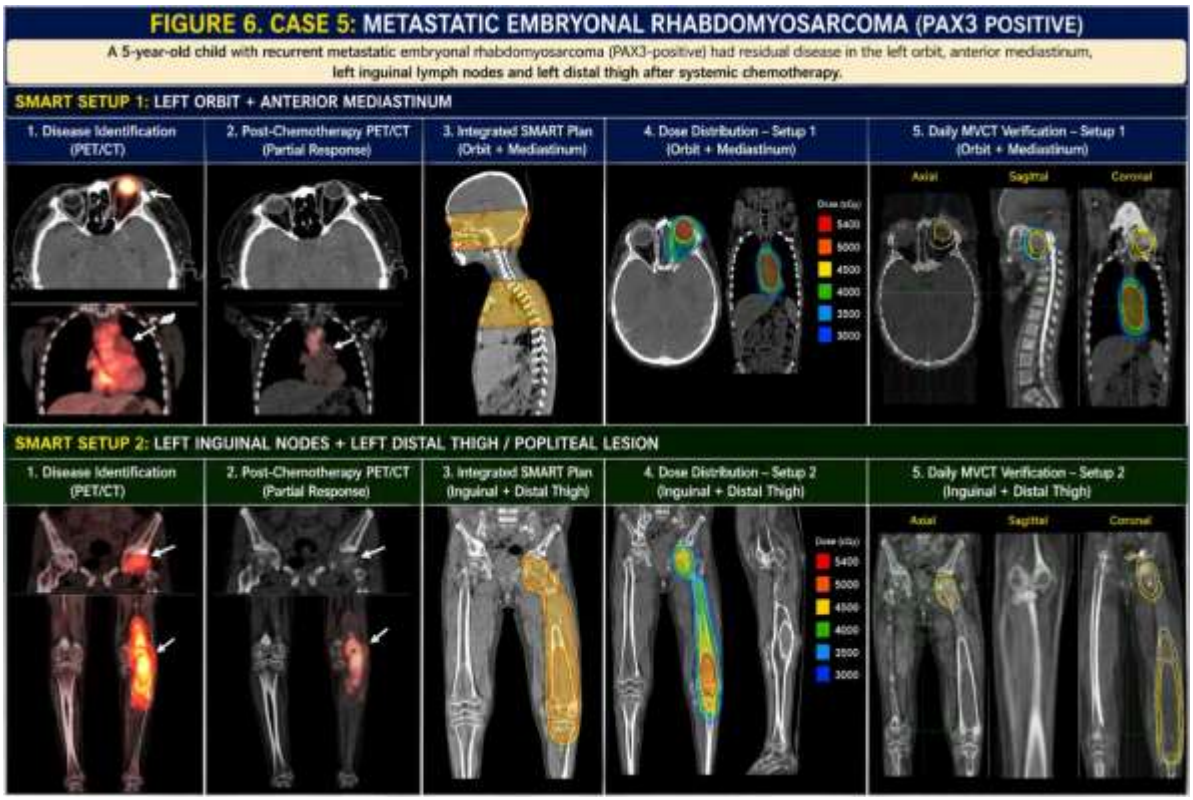
Case 4. Metastatic Lung Cancer

A 69-year-old man with metastatic carcinoma of the left lung had symptomatic metastases involving the **brain, left scapula, and right iliac bone**. The **SMART** workflow was implemented using **two treatment setups**: the **first setup** delivered **whole-brain radiotherapy (30 Gy in 10 fractions)** for multiple brain metastases, while the **second setup** simultaneously treated the **left scapula and right iliac bone (20 Gy in 5 fractions each)** for pain relief and local disease control. Daily MVCT image guidance ensured accurate and reproducible treatment delivery for both treatment setups.



Case 5. Metastatic Embryonal Rhabdomyosarcoma

A 5-year-old child with recurrent metastatic **embryonal rhabdomyosarcoma (PAX3-positive)** had residual metastatic disease involving the **left orbit, anterior mediastinum, left inguinal lymph nodes, and left distal thigh** after systemic chemotherapy. The **SMART** workflow was implemented using **two treatment setups**, with the **first setup** treating the **orbital and mediastinal lesions** and the **second setup** treating the **inguinal nodal and left distal thigh lesions**. Daily MVCT image guidance ensured precise and reproducible treatment delivery.



4.DISCUSSION

4.1 Technical Rationale and Workflow Advantages

The increasing adoption of stereotactic body radiotherapy (SBRT) has fundamentally changed the management of oligometastatic disease by enabling delivery of ablative radiation doses with excellent local control while minimizing toxicity to surrounding normal tissues. Landmark randomized trials including SABR-COMET, ORIOLE, STOMP, and EXTEND have established metastasis-directed SBRT as an important component of multidisciplinary treatment for selected patients with oligometastatic disease, leading to a growing demand for efficient delivery of radiotherapy to multiple metastatic lesions. [7-10] Despite these advances, treatment complexity increases considerably when multiple

lesions require irradiation during the same treatment course. Conventional C-arm linear accelerator workflows generally require separate isocenters, repeated patient positioning, multiple cone-beam CT (CBCT) acquisitions, independent treatment plans, and sequential irradiation of each lesion. Although these techniques achieve excellent geometric precision, they prolong treatment duration, increase machine occupancy, and may contribute to cumulative setup uncertainty associated with repeated positioning and image-guided verification. [15]

Table 4. Technical Comparison Between Conventional Multi-Isocenter SBRT and SMART

Parameter	**Conventional Multi-Isocenter SBRT**	**SMART Workflow**
Patient setup	Multiple	Single (or one per standardized setup)
Planning CT	Separate CT for each isocenter	One CT per SMART setup
Immobilization	Repeated	Single per setup
Treatment planning	Multiple independent plans	One integrated plan per setup
Isocenters	Multiple	Integrated helical workflow
Image guidance	Multiple CBCTs	Single MVCT per setup
Patient repositioning	Required	Not required within each setup
Beam delivery	Sequential	Continuous helical delivery
Target optimization	Individual	Simultaneous
Workflow complexity	High	Standardized
Patient comfort	Lower	Improved
Machine efficiency	Lower	Higher

Table 4 summarizes the fundamental technical differences between conventional multi-isocenter SBRT and the SMART workflow.

The SMART (**S**ingle-**S**etup **M**ulti-**T**arget **A**ccurate **R**adiation **T**herapy) framework was developed to directly overcome these operational workflow limitations. Rather than introducing a novel hardware platform, SMART represents a standardized technical protocol that leverages the inherent capabilities of Helical TomoTherapy to streamline multi-target stereotactic treatments. This approach consolidates all targetable metastatic lesions into a unified workflow: a single simulation, one immobilization strategy, a single planning CT dataset, one inverse-optimized treatment plan, a single MVCT-guided verification, and one uninterrupted treatment delivery slot. By eliminating repetitive setup steps while rigorously maintaining stereotactic precision, SMART offers a highly practical framework for comprehensive multi-target irradiation.

A major clinical benefit of the SMART protocol is institutional workflow standardization. Modern stereotactic radiotherapy demands a complex sequence of distinct processes, including patient selection, immobilization, multimodality image registration, target contouring, treatment planning, quality assurance, image guidance, and delivery. Variability at any point along this clinical pathway can compromise treatment reproducibility. SMART mitigates this by establishing a structured, uniform protocol for every stage of care, which promotes consistent execution, minimizes inter-operator divergence, and strengthens quality assurance frameworks within high-volume stereotactic radiotherapy clinics.

The practical feasibility of the SMART workflow is fundamentally tied to the unique architectural design of the Helical TomoTherapy platform.

Unlike conventional C-arm linear accelerators, Helical TomoTherapy combines continuous rotational intensity-modulated radiation therapy (IMRT) with synchronized couch translation and integrated megavoltage computed tomography (MVCT) image guidance. This configuration enables anatomically separated lesions to be incorporated into a single inverse-optimized treatment plan while maintaining highly conformal dose distributions and steep dose gradients around adjacent critical structures. Continuous helical beam delivery also eliminates the need for repeated gantry repositioning or multiple isocenter arrangements, thereby simplifying treatment of complex multi-target cases. [16-21] Daily MVCT-guided verification represents another important component of the SMART workflow. Accurate localization before each stereotactic treatment fraction is essential because ablative doses are delivered using narrow planning target volume margins. On-board MVCT permits volumetric assessment of patient anatomy immediately before treatment, allowing translational corrections to be performed before irradiation. [18-20]. In contrast to conventional multi-isocenter workflows that frequently require repeated CBCT acquisitions, SMART employs a single volumetric image-guided verification encompassing all target lesions, thereby improving workflow efficiency while maintaining stereotactic accuracy.

An additional advantage of SMART is its applicability across diverse clinical scenarios. Because the workflow is independent of tumour histology or metastatic location, it can be applied to patients with synchronous pulmonary, hepatic, adrenal, lymph node, vertebral, pelvic, and non-spinal skeletal metastases, provided cumulative organ-at-risk constraints remain acceptable. The representative clinical applications presented in this report demonstrate that the same standardized

workflow can be successfully implemented across different primary malignancies and anatomical distributions without modification of the overall treatment strategy.

Importantly, SMART should not be considered simply as a method for reducing treatment time. Its principal objective is to provide a reproducible technical framework for delivering comprehensive multi-target stereotactic radiotherapy while maintaining the precision, safety, and dosimetric quality expected of modern SBRT. Consistent with recent ASTRO-ESTRO clinical practice recommendations, careful multidisciplinary patient selection, integration with systemic therapy, and technically safe treatment of all intended metastatic sites remain fundamental prerequisites for successful implementation [35]. Consequently, SMART should be regarded as a workflow innovation that complements established stereotactic radiotherapy principles rather than replacing current evidence-based treatment guidelines.

4.2 Clinical Evidence Supporting the SMART Workflow

Although SMART represents a standardized technical workflow rather than a novel radiation delivery platform, its development is strongly supported by the growing body of literature describing the successful application of Helical TomoTherapy for the treatment of multiple metastatic lesions. Published institutional experiences consistently demonstrate that Helical TomoTherapy provides excellent target conformity, reliable image guidance, and acceptable toxicity when treating anatomically separated lesions across diverse clinical settings [22-16] . These studies collectively establish the technical foundation upon which SMART has been developed. Among the foundational publications, Soo et al. demonstrated the clinical feasibility of using image-guided Helical TomoTherapy for patients requiring concurrent irradiation of multiple metastatic lesions within a single treatment course [22]. Their data confirmed that integrated treatment planning could safely achieve conformal dose distributions, maintaining satisfactory target coverage alongside acceptable toxicity profiles. While this early experience predated the contemporary definition of oligometastatic SBRT, it successfully established the baseline principle that multiple distinct metastatic sites could be consolidated into a single Helical TomoTherapy treatment strategy.

Subsequent technological iterations in multimodality imaging, inverse planning optimization algorithms, and daily MVCT image guidance have significantly enhanced both the precision and reproducibility of the Helical TomoTherapy platform. Building upon these technological refinements, Yamada et al. reported encouraging local control rates with minimal high-grade toxicities in a cohort of patients with chemotherapy-refractory or chemotherapy-unfit disease presenting with three or more metastatic lesions [23]. Their clinical outcomes demonstrated that comprehensive irradiation of multiple, anatomically separated targets could be executed safely despite elevated treatment complexity, further validating the rationale for single-course, multi-target radiotherapy.

The clinical versatility of Helical TomoTherapy has been similarly observed in anatomically challenging disease sites. For instance, in patients presenting with multiple liver metastases, Yamada et al. showed that highly conformal stereotactic irradiation could be delivered while preserving uninvolved liver parenchyma and maintaining acceptable toxicity.[24] More recent reports have extended these observations to **peritoneal and abdominal wall oligometastases**, where continuous helical delivery achieved excellent dose conformity around irregular target volumes with satisfactory organ-at-risk sparing,[25] and to **non-spinal skeletal oligometastases**, where image-guided SBRT produced excellent local control with minimal treatment-related toxicity[26]

Although these studies evaluated different clinical scenarios, they consistently demonstrate that Helical TomoTherapy is capable of safely treating multiple metastatic lesions distributed across different anatomical regions. However, the published literature has largely focused on the feasibility of individual disease sites rather than describing a standardized workflow. SMART expands upon these experiences by integrating patient selection, multimodality imaging, immobilization, inverse treatment planning, quality assurance, image-guided verification, and treatment delivery into one reproducible clinical pathway.

Table 5. Published Clinical Evidence Supporting the Development of SMART Using Helical TomoTherapy

Ref	Study	Clinical Setting	Major Technical Findings	Contribution to SMART
22	Soo RA et al. *Int J Radiat Oncol Biol Phys.* 2009	Multiple metastatic lesions	Demonstrated feasibility of integrated image-guided Helical TomoTherapy with satisfactory target coverage and acceptable toxicity.	Established the technical feasibility of treating multiple metastatic lesions within one Helical TomoTherapy treatment course.
23	Yamada Y et al. *Rep Pract Oncol Radiother.* 2022	≥3 chemotherapy-refractory/unfit metastases	Encouraging local control with low severe toxicity despite multiple anatomically separated lesions.	Supports comprehensive multi-target irradiation during a single treatment course.
24	Yamada Y et al. *Cancer Medicine.* 2019	Multiple liver metastases	Demonstrated safe delivery of highly conformal liver SBRT while preserving normal liver tissue.	Validates integrated planning for complex visceral targets.

Ref	Study	Clinical Setting	Major Technical Findings	Contribution to SMART
25	*J Pers Med.* 2025	Peritoneal and abdominal wall oligometastases	Excellent conformity and organ-at-risk sparing for irregular abdominal targets.	Supports SMART for anatomically complex abdominal disease.
26	*Clin Transl Oncol.* 2026	Non-spinal bone oligometastases	Excellent local control with minimal toxicity using image-guided SBRT.	Demonstrates applicability of SMART for multifocal skeletal metastases.

Collectively, these studies demonstrate that Helical TomoTherapy provides the technical capability to safely treat multiple metastatic lesions with excellent dosimetric quality. SMART builds upon this evidence by providing a standardized workflow that simplifies implementation, improves reproducibility, and facilitates routine clinical application of comprehensive multi-target stereotactic radiotherapy.

4.3 Contemporary Perspective, Limitations and Future Directions

The role of metastasis-directed radiotherapy continues to evolve rapidly with the publication of several contemporary randomized clinical trials. Recent studies including **RADIOSA**, **ARTO**, **STOP**, **MITO-RT3/RAD**, and prospective investigations in oligometastatic renal cell carcinoma have further demonstrated that comprehensive SBRT can delay systemic therapy, prolong progression-free survival, and improve disease control across different oligometastatic states. [27-33]These findings reinforce the growing importance of efficient and reproducible treatment workflows capable of delivering high-quality multi-target radiotherapy.

SMART should therefore be viewed as a technical workflow designed to facilitate implementation of comprehensive metastasis-directed radiotherapy rather than to expand current treatment indications. Contemporary ASTRO-ESTRO clinical practice guidelines emphasize careful multidisciplinary patient selection, integration with systemic therapy, and technically safe treatment of all intended metastatic sites. [35] These principles closely align with the SMART workflow, which seeks to standardize the complete treatment pathway while maintaining stereotactic precision.

An additional advantage of SMART is its potential to improve integration of radiotherapy with modern systemic therapies. Simplified treatment logistics may reduce interruptions to chemotherapy, targeted therapy, and immunotherapy while improving coordination of multidisciplinary care. Experimental evidence has demonstrated that SBRT induces immunogenic cell death, activation of the cGAS-STING pathway, and enhanced tumour antigen presentation. [11-14] Although SMART has not yet been shown to augment systemic immune responses directly, simultaneous irradiation of multiple metastatic lesions may provide an attractive platform for future investigations combining comprehensive SBRT with immune checkpoint inhibitors.

Several limitations should be acknowledged. SMART requires meticulous patient selection, experienced treatment planning, rigorous quality assurance, and strict adherence to established SBRT contouring and organ-at-risk constraints. The workflow may not be appropriate for patients with excessive respiratory motion, very large cumulative target volumes, previous overlapping irradiation, or anatomical situations where treatment length becomes impractical. Furthermore, although one image-guided setup simplifies treatment delivery, careful verification of regional anatomical alignment remains essential, particularly when lesions are widely separated. International SBRT recommendations should continue to guide contouring, image guidance, and dose constraints, especially for spinal and other critical anatomical sites. [6,36]

The present report should also be interpreted within the context of its design. SMART represents a **technical innovation** rather than a prospective clinical trial, and therefore does not establish superiority over conventional multi-isocenter SBRT techniques. Future multicentre prospective studies are required to evaluate treatment efficiency, planning time, overall treatment duration, patient-reported comfort, dosimetric quality, toxicity, local control, progression-free survival, and cost-effectiveness. Comparative studies with modern LINAC-based multi-isocenter and single-isocenter techniques will further define the clinical role of SMART in contemporary stereotactic radiotherapy.

TABLE 6 Advantages and Limitations of SMART

Advantages	Limitations
Standardized workflow	Requires Helical TomoTherapy
Single integrated planning	Longer delivery time for extensive targets
Reduced patient repositioning	Careful patient selection required
Daily volumetric image guidance	Requires experienced planning team
Improved workflow efficiency	Not suitable for all target distributions
Excellent target conformity	Complex cases may require multiple setups
Improved patient comfort	Requires rigorous QA

TABLE 7 Potential Future Applications of SMART

Clinical Scenario	Potential Role of SMART
Oligometastatic disease	Current application
Oligoprogressive disease	Potential application
Multiple bone metastases	Demonstrated
Pediatric metastatic disease	Demonstrated
Synchronous primary malignancies	Potential application
SBRT combined with immunotherapy	Future research
Adaptive radiotherapy	Future integration
AI-assisted treatment planning	Future development

CONCLUSION

SMART (Single-Setup Multi-Target Accurate Radiation Therapy) is a standardized technical workflow for delivering stereotactic radiotherapy to multiple metastatic lesions using Helical TomoTherapy. By integrating single simulation, single immobilization, one planning CT dataset, one inverse-optimized treatment plan, one MVCT-guided verification, and one continuous treatment session, SMART provides a practical and reproducible approach for comprehensive multi-target stereotactic radiotherapy.

The representative clinical applications presented in this report demonstrate the technical feasibility and versatility of SMART across diverse anatomical sites and tumour types. The workflow simplifies the delivery of technically complex multi-target treatments while maintaining the geometric precision, image-guided accuracy, and dosimetric quality required for stereotactic radiotherapy. In addition, SMART has the potential to improve workflow efficiency, reduce cumulative setup uncertainty, enhance patient comfort, and optimize departmental resource utilization.

Although this report focuses on technical implementation rather than comparative clinical outcomes, SMART establishes a standardized framework for single-setup, multi-target stereotactic radiotherapy using Helical TomoTherapy. Prospective multicentre studies are warranted to evaluate its impact on treatment efficiency, dosimetric quality, toxicity, patient-reported outcomes, local control, and cost-effectiveness.

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