ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Biology-guided radiotherapy for treatment of lung or bone tumours in adults

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Contents

Summary of Key Points

- Lung cancer is the third most common malignancy and the leading cause of cancer death in Singapore. Approximately 65% of patients are diagnosed at Stage IV, which has a 5-year survival rate of less than 10%.
- Bone is the third most common site of cancer spread, affecting 30 to 40% of advanced lung cancer patients and up to 80% of those with advanced breast or prostate cancer.
- Standard stereotactic body radiotherapy (SBRT) utilises motion-encompassing volumes to treat moving targets for tumour destruction and pain control. However, treating a moving target involves irradiating a larger volume of normal tissue, which comes with risks such as radiation pneumonitis.
- SCINTIX biology-guided radiotherapy (BgRT) is an FDA-approved system that integrates positron emission tomography (PET) detection with a linear accelerator to use real-time 18F-fluorodeoxyglucose (FDG)-PET signals from the tumour to guide the beam. It is approved by FDA for the treatment of adults with lung or bone tumours that are subject to motion and positional uncertainty. This biological tracking, delivered in ≤5 fractions, allows for tighter margins, and aims to reduce the damage to healthy lung and bone tissues that move during respiratory motion.
- Based on limited evidence including one prospective single-arm study, two abstracts of a registry study and a case series, and the FDA *De Novo* summary, SCINTIX was found to be generally safe and showed some benefits in treating lung and bone tumours that are subject to motion and positional uncertainty. Following treatment with SCINTIX,
    - Adverse events occurred in more than half of the patients studied, although they were not considered to be treatment related.
    - For patients with both lung and bone targets (n=45), interim registry data showed 100% local control at 9 months.
    - For patients with bone metastases (n=10), 80% achieved complete pain response at a median follow-up of 5.1 months and there was a 65.8% median reduction in maximum standardised uptake value (a functional success measure)
- There is a lack of comparative study comparing SCINTIX directly to standard SBRT. Current data are derived mostly from western academic centres.
- No cost-effectiveness evidence is available. The technology is estimated to cost S$13 million, but further detailed pricing information is not available.
- SCINTIX requires intense interdisciplinary coordination for delivering FDG in a timely manner. Total interdisciplinary session times are longer than standard volumetric modulated arc therapy (which typically takes 5-10 minutes), as they include a 60 to 90 minutes tracer uptake period, followed by specialised PET pre-scanning and real-time tracking delivery. Such extended workflow may impact patient throughput in public healthcare institutions.

- Various radiotherapy systems are evolving to address the clinical challenge of intrafractional motion including Unity BgRT Enhancement (Elekta) and CyberKnife Synchrony system, which rely on anatomical surrogates for treatment guidance.
- The ongoing PREMIER registry (NCT05406167) involving 750 patients, is expected to provide some safety, effectiveness and economic data in 2026.
- Clinicians anticipated low clinical need for SCINTIX BgRT, as the current standard of care provides sufficient outcomes for most patients.

I. Background

Lung and bone cancers are heterogeneous diseases characterised by uncontrolled cell growth in lung or bone tissues, respectively. Lung cancer is broadly classified into non-small cell lung cancer (NSCLC; about 85% of all lung cancer cases) and small cell lung cancer (SCLC).[1] Bone cancer is broadly classified into chondrosarcoma (about 40% of adult cases), osteosarcoma (about 25%), chordoma (about 10%), and Ewing sarcoma (about 8%). Less common types include giant cell tumour of bone and undifferentiated pleomorphic sarcoma.[2] These cancers are staged from early (I-II) to locally advanced (III) and metastatic (IV).[2-4]

The burden of both lung and bone cancers remains high in Singapore. Lung cancer is the third most common malignancy in Singapore, the top cause of cancer-related mortality in males (24.6%) and the third highest in females (15.9%).[5] Approximately 65% of lung cancer patients are diagnosed at a stage where metastasis has already developed and 5-year survival rates are below 10%.[5] While bone is the third most common site of cancer spread, primary bone cancers are rare, accounting for less than <1% of adult cancers.[6, 7] Bone metastasis occur in up to 80% of patients with advanced breast or prostate cancer[8] and in 30 to 40% of patients with advanced NSCLC.[9] Beyond primary sites, there may be up to 15,150 patients with metastatic bone disease in Singapore.[5, 10]

Patients with advanced NSCLC often have compromised lung capacity, making surgical options difficult and increasing the importance of non-invasive local therapies. Bone metastasis often require localised interventions to maintain skeletal integrity and quality of life. While systemic therapy is the first-line treatment for metastatic disease, localised standard stereotactic body radiotherapy (SBRT) is necessary for tumour destruction and pain control.[2-4] SBRT uses motion-encompassing volumes (internal target volume; ITV) created via computed tomography (CT) to treat moving targets.[11] This approach carries important risks for patients with limited reserves. In lung tumours, the approach risks radiation pneumonitis (5–20% risk)[12], which is particularly dangerous for those with already compromised lung capacity, as it causes severe breathlessness and permanent fibrosis.[12] In bone metastases of the ribs or thoracic spine, which move with breathing, large margins increase the risk of pathological fractures and potential damage to the spinal cord and liver.[13-15] For these patients, there is a clinical need for a tracking technology that can reduce these margins by adapting to real-time biological signals, to spare healthy tissue while maintaining high-dose efficacy.

II. Technology

SCINTIX (RefleXion Medical Inc.) is the biology-guided radiotherapy (BgRT) modality within the RefleXion Medical Radiotherapy System (RMRS).[16] The RMRS is a hybrid platform that combines the functionality of a positron emission tomography (PET) detection system with a megavoltage X-ray linear accelerator. While the system retains full capability for delivering conventional SBRT, the SCINTIX modality specifically enables 18F-fluorodeoxyglucose (FDG)-guided beam delivery.[16]

This BgRT follows a special radiopharmaceutical protocol whereby prior to the treatment session, the patient receives an intravenous injection of FDG. Following the injection, a 60-minute uptake period is required to ensure consistent biodistribution. This protocol must be followed before the initial planning session and prior to each subsequent treatment fraction. The minimum criteria for starting BgRT are a tumour activity concentration (AC) of ≥5 kBq/mL and a normalised target signal (NTS) ≥2.0 at the time of delivery.[16]

While conventional SBRT relies on pre-treatment imaging (CT or PET) to define a target for the fractions, SCINTIX utilises two PET detector arcs integrated with an automatic tracking algorithm to autonomously guide dose delivery in real-time. Whereas the target of conventional SBRT is a wide area that considers all potential positions the tumour might occupy during the treatment session, SCINTIX uses the FDG emission signal to direct the fraction to the tumour as it moves, sparing a larger volume of healthy tissue without compromising on efficacy.

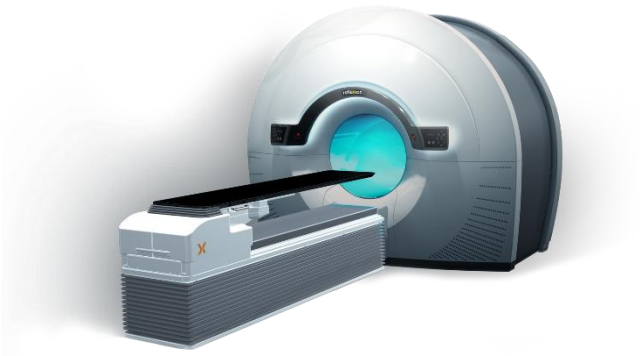

Figure 1: Illustration of SCINTIX. Image adapted from Presentations at American Society for Radiation Oncology 2021, RefleXion.[31]

III. Regulatory and Subsidy Status

SCINTIX is a U.S. Food and Drug Administration (FDA)-classified FDG-guided radiation therapy system integrating PET with a linear accelerator.[16] It is authorised for the treatment, in five or fewer fractions, of adults with lung or bone tumours (primary or metastatic) that are subject to motion and positional uncertainty. Use of this system is contingent on adequate localisation and FDG uptake, which is assessed in advance with on-board PET/CT.[16] BgRT is a distinct device category indicated for FDG-guided radiotherapy under motion.[16] RMRS received a Breakthrough Device Designation from the FDA in 2021, and De Novo marketing

authorisation in February 2023, clearing SCINTIX for the delivery of BgRT. This clearance also covers the use of FDG (the most common PET tracer) as the guiding biological signal during treatment.

In the United States, the Centers for Medicare & Medicaid Services cover BgRT treatment planning and delivery in both hospital outpatient and freestanding cancer centre settings,[17] with a national payment rate of US$1,950.50 (S$2,507)[a] and US$3,750.50 (S$4,820)[a] per session, respectively.[18] As of January 2026, SCINTIX has not yet been registered with the Health Sciences Authority (HSA) for use in Singapore.

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

Local clinical practice largely follows the National Comprehensive Cancer Network (NCCN) guidelines.[2-4] In general, in both lung and bone cancers, standard practice includes surgery, systemic therapy, or radiation therapy (RT), depending on staging. As per the lung cancer clinical pathway (See Figure B1 in Appendix B), any patient with lung cancer, including those with NSCLC (Stage I-IV) and SCLC (limited or extensive stage), is eligible to receive RT as part of their treatment plan. Similarly, based on the bone cancer pathways (See Figure B2 and B3 in Appendix B), RT is a treatment option for all patients with bone cancer except those with low-grade osteosarcoma, who are primarily managed via surgery.[2] While the clinical pathways outline various roles for RT, local experts note that surgery remains the curative mainstay for primary bone tumours with SBRT is a treatment option in complex bone metastases or in oligo-metastatic disease states (Personal communication: Radiation Oncologist from NCIS, December 2025, February 2026).

As per the FDA, SCINTIX is indicated for patients where RT is recommended, and three specific criteria are met: the treatment is intended to be delivered in ≤5 fractions; the lesion is FDG-avid; and there is positional uncertainty (as shown in the decision overlay in the treatment algorithms).[16] Local experts expressed that the patients eligible to receive SCINTIX would be

[a] Based on the Monetary Authority of Singapore exchange rate as of 20 January 2025: US$1=S$1.2852. Figures were rounded to the nearest dollar.

the same as those eligible to receive SBRT, which is aligned with the indication for SCINTIX in ≤5 fractions, a standard convention for SBRT.

Thus, it was suggested that in local practice, SCINTIX could potentially be used in patients with medically inoperable early-stage NSCLC (T1-2 N0, as per the TNM Staging System) and metastatic lung or bone tumours. (Personal communication: Radiation Oncologist from NCIS, December 2025)

VI. Summary of Evidence

This assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria outlined in Table 1. Literature searches were conducted in Cochrane Library, Embase, PubMed, Scopus, and EconLit. The selection process is detailed in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Flow Diagram (See Figure A1 in Appendix A). The key evidence base of clinical studies that align with the proposed PICO is limited and derived exclusively from single-arm studies. This includes one full peer-reviewed publication of a pivotal Phase I, first-in-human trial (BIOGUIDE-X (NCT04788147); n=17)[19], and two conference abstracts: one prospective multi-centre registry study (PREMIER registry (NCT05406167); n=45)[20], and one prospective case series (n=10).[21] All clinical studies included patients with lung or bone tumours (primary or metastatic) eligible for SBRT. Extensive technical validation was identified as supplementary evidence, including five retrospective dosimetric planning studies (all abstracts)[22-25] and seven phantom-based tracking simulations[24, 37-42], comprising four abstracts[26-29] and three full publications.[30-32] A complete list of included studies and their study design characteristics are in Appendix A, with additional information on dosimetric and phantom studies in Appendix C.

Table 1. PICO criteria

Population	Adults with lung or bone tumours (primary or metastatic)
Intervention	Biology-guided radiotherapy
Comparator	Stereotactic body radiotherapy
Outcome	Safety, clinical-effectiveness and cost-effectiveness

Safety

Only two primary studies (BIOGUIDE-X trial and the PREMIER registry) reported evidence on the safety of SCINTIX (Table 2). The safety outcomes from BIOGUIDE-X were reported in the FDA De Novo Summary (DEN220014)[16] and the peer-reviewed publication by Vitzthum et al. (2024).[19] While both reported identical values for overlapping outcomes, the DEN220014 document provides a higher level of granularity. For this reason, the publication by Vitzthum et al. (2024) has been omitted from Table 2.[19] The PREMIER registry were available from an abstract presenting interim results.[20]

Across these sources, the safety profile was favourable with no reported treatment-related adverse events (TRAEs) or FDG-related toxicities(Table 2).[16, 19, 20] Treatment-emergent adverse events (TEAEs) were observed in approximately half of the participants of BIOGUIDE-

X.[16] Furthermore, it is critical to note that the BIOGUIDE-X trial used emulated delivery (in silico) rather than an active RT.[16]

Table 2. Safety outcomes related to SCINTIX

Study	Population (n)	Outcomes	Effect estimates
Dan et al. (2025)[20]	n = 45 (Lung/Bone Cancer)	Serious TRAE TRAE Grade ≥ 2 AE	0% (0/45) 0% (0/45)
FDA DEN220014 [BIOGUIDE-X trial][16, 19]	n = 17 (Lung/Bone Cancer)	Any TRAE FDG-related AE[a] Any TEAE[b] Musculoskeletal Lab abnormalities Gastrointestinal Fatigue Anaemia Decreased appetite Somnolence Pollakiuria Prostatic obstruction Pain of skin Discontinuation due to AE	0% (0/17) 0.1% (1/17) 58.8% (10/17) 35.3% (6/17) 17.6% (3/17) 17.6% (3/17) 11.8% (2/17) 5.9% (1/17) 5.9% (1/17) 5.9% (1/17) 5.9% (1/17) 5.9% (1/17) 5.9% (1/17) 0% (0/17)

Note:

[a] Vitzthum (2024) stated that there was 1 TEAE considered probably related to FDG exposure (oral dysesthesia, grade 1). It resolved on the same day without treatment and did not result in any action on the study device or the discontinuation of any participant from the study.[14] The FDA DEN220014 didn't consider this evidence in the authorisation decision.[13]

[b] TEAE was defined as any AE that started on or after the first dose of FDG or occurred prior to the first dose and worsened in severity on or after the first dose of FDG, during the treatment period and follow-up period.

Abbreviations: AE, adverse event; FDA, U.S. Food and Drug Administration; FDG, fluorodeoxyglucose; n, number of participants; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Effectiveness

Only two abstracts were identified as key evidence base reporting evidence on the efficacy of SCINTIX, the prospective case series by Wang et al. (2025)[21] and the PREMIER registry (interim results)[20] (Table 3). No evidence on efficacy was reported as part of the BIOGUIDE-X trial.[16, 19] As part of the supplementary evidence, five retrospective dosimetric planning studies[22-25] and seven phantom-based tracking simulations were included.[26-32] These phantom-based studies used physical or computer-simulated models replicating patient anatomy and motion to enable controlled evaluation of SCINTIX.

Tumour Response and Pain Relief

Overall, SCINTIX demonstrated a positive tumour response profile.[20, 21] Interim results from the PREMIER registry, which enrolled patients with both lung or bone targets (n=45) showed that participants maintained a 100% local tumour control rate at a median follow-up of 9 months.[20] This metric serves as an aggregate anatomical success measure, that includes all

patients who achieved a complete response, a partial response, or stable disease (Table 3 footnotes for detailed definitions).

In the prospective case series focusing on patients with bone metastases (n=10), a 65.8% reduction in maximum standardised uptake value (SUV_{max}), a functional success measure, was observed.[21] Additionally, in the same study, 80% of patients achieved complete pain response at a median follow-up of 5.1 months.[21]

Table 3 Clinical Efficacy Outcomes of SCINTIX

Study	Population (n)	Outcomes	Result
Dan et al. (2025)[20]	n = 45 (Lung/Bone)	Local Tumour Control (Anatomical)[a] Tumour Response (Anatomical)[b]	100% at 9 months 9.5% CR; 38.1% PR; 52.4% SD
Wang et al. (2025)[21]	n = 10 (Bone Mets)	Metabolic Response (Functional)[c] Pain Relief (Symptomatic)[d]	65.8% reduction in SUV_{max} 80% Complete; 20% Partial

Note:

[a] Local Tumour Control is defined in the PREMIER registry as the absence of local recurrence at the treated site and reported as the aggregate proportion of patients achieving a complete response, partial response, or stable disease.

[b] Tumour Response was assessed by local investigators or multidisciplinary tumour boards using follow-up imaging (CT or PET/CT). Complete Response indicates the disappearance of the target lesion; Partial Response indicates a significant decrease in tumour burden; and Stable Disease indicates neither sufficient shrinkage to qualify as a response nor sufficient growth to qualify as progression.

[c] Metabolic Response was categorised using the PET Response Criteria in Solid Tumours (PERCIST). Success is determined by quantitative changes in biological activity, specifically the reduction in SUV_{max}.

[d] Symptomatic Relief was evaluated as a patient-reported pain response. Complete Pain Response refers to the total disappearance of pain at the treated site, while Partial Pain Response indicates a significant reduction in pain intensity.

Abbreviations: CR, complete response; CT, computed tomography; Mets, metastases; n, number of participants; PET, positron emission tomography; PERCIST, PET Response Criteria in Solid Tumours; PR, partial response; SD, stable disease; SUV_{max}, maximum standardised uptake value.

Technical and Dosimetric Performance

With a delivery feasibility rate of 94.1%, SCINTIX was reported to accurately calculate and execute radiation dose in real-time based on the biological signals (PET emissions) from the tumour.[19]

Supplementary evidence demonstrated that SCINTIX had superior technical precision compared to standard SBRT planning techniques (Table C1 in Appendix C). Comparative dosimetric studies also reported reductions in planning target volumes (PTV), the area that receives the full prescription dose of radiation, that ranged from 21.5% to 32.3%[23-25], and a reduction of 4.4% in healthy lung tissue exposure.[23] Additional phantom studies demonstrated successful tracking of moving targets with minimal margin loss (<3 mm).[33] Detailed procedure-related outcomes and study-specific results are provided in Appendix C.

Cost-effectiveness

No cost-effectiveness studies for SCINTIX therapy were identified.

Ongoing clinical trials

A scan of ClinicalTrials.gov (as of January 2026), ICTRP, and Cochrane Central Register of Controlled Trials identified three ongoing trials evaluating SCINTIX (Table 4). The largest trial is the manufacturer-sponsored PREMIER Registry, a prospective multi-cohort study that is expected to generate comparative evidence (including health economic outcomes) with its three-treatment-arm design (BgRT, SBRT, and intensity-modulated radiation therapy [IMRT]).

Two smaller investigator-initiated trials are also underway: a Phase 1 pilot study evaluating the safety of single-fraction BgRT for painful bone metastases (NCT06549478), and a Phase 2 trial assessing the potential of BgRT to extend the efficacy of concurrent osimertinib in oligoprogressive epidermal growth factor receptor (EGFR)-positive NSCLC (NCT06014827). These studies are single-arm and limited in sample size, precluding definitive comparative effectiveness conclusions.

Table 4 Ongoing clinical trials

Study (Trial ID)	Population	Brief description	Estimated study completion date
PREMIER Registry (NCT05406167)[34]	Patients with local, loco-regionally advanced, or oligometastatic malignancies undergoing radiotherapy (n=750)	A large-scale prospective observational registry collecting real-world data on clinical outcomes (survival, recurrence), toxicity, quality of life, and health economic impact of the RefleXion system (IMRT, SBRT, and SCINTIX).	April 2026
Biology-Guided Radiation Therapy for Bone Metastases (NCT06549478)[35]	Patients with painful bone metastases (n=24)	A Phase 1 interventional trial evaluating the safety and pain response of a single-fraction SCINTIX treatment for bone metastases.	January 2027
BgRT and SBRT with Osimertinib for Oligoprogressive Lung Cancer (NCT06014827)[36]	Patients with oligoprogressive EGFR-positive non-small cell lung carcinoma (n=32)	A Phase 2 trial assessing the efficacy of combining SCINTIX (for active lesions) and standard SBRT with the tyrosine kinase inhibitor osimertinib to treat oligoprogressive disease.	July 2026

Abbreviations: BgRT, biology-guided radiotherapy; EGFR, epidermal growth factor receptor; IMRT, intensity-modulated radiotherapy; n, number of participants; NCT, National Clinical Trial identifier; SBRT, stereotactic body radiotherapy.

Summary

Based on the limited available evidence, SCINTIX was found to be generally safe, with a favourable profile regarding TRAE and one TEAE considered probably related to FDG exposure. In terms of effectiveness, limited evidence showed that SCINTIX demonstrated high tumour response based on anatomical (100% local tumour control), functional (65.8% median reduction in SUV_{max}) and symptomatic measures (80% of patients achieving complete pain response). The cost-effectiveness evidence of SCINTIX in the treatment of lung and bone tumours is lacking.

Supplementary technical evidence highlights superior dosimetric precision of SCINTIX compared to SBRT, with reductions in PTV of up to 32.3% and improved sparing of healthy lung tissue.

The evidence should be interpreted with caution. Key evidence gaps include the small, single-arm studies without a control group, as well as a lack of long-term data regarding local recurrence, survival rates, and quality of life. Furthermore, the applicability of the results to the local population remains uncertain, as the clinical evidence base is predominantly derived from academic centres. It is also worthwhile highlighting that all the studies forming the key evidence base were funded by the manufacturer of SCINTIX.

Ongoing research, specifically the large-scale PREMIER registry (n=750), is expected to generate some important comparative evidence, on safety, efficacy, and health economic outcomes.

VII. Estimated Costs

The capital cost of SCINTIX was not identified, but overseas media have reported that RefleXion's SCINTIX BgRT may cost ~US$10 Million (S$13 Million)[b].[37]

VIII. Implementation Considerations

Adopting SCINTIX would require several changes to treatment planning and execution and could introduce operational challenges. A time-motion study indicates that the SCINTIX process is more resource-intensive than conventional methods, with an average injection-to-scan time of 84 ± 19 minutes (including the mandatory 45-60 minutes radiotracer uptake period), with a beam delivery time of 27 ± 5 minutes.(38) In comparison, the standard SBRT delivery through volumetric modulated arc therapy is typically completed within 5-10 minutes. This extended duration could limit daily patient throughput. In terms of reliability, the SCINTIX system showed a 92% machine uptime in its first year of clinical operation, with 72 unscheduled downtime events.(39)

Additionally, the operational implementation of SCINTIX requires high-level coordination between the radiotherapy and nuclear medicine departments, as the latter manages FDG. Due to the relatively short half-life of FDG (approximately 60 minutes), compounded by mandatory adherence to radioprotection protocols, planning is essential to synchronise the injection time with the fraction delivery time. Long delays can render the tracer unusable, resulting in re-administration or cancellation of the treatment session. (Personal communication: Radiation Oncologist from NCIS, 10 December 2025). This also means that for centres without an on-site cyclotron, which is necessary for producing FDG, the timely delivery of FDG would be a major operational dependency for daily SCINTIX use. It is notable that a new dose of FDG needs to be injected before every fraction.

A further consideration for SCINTIX is the necessary adaptation of standard radiotherapy

[b] Based on the Monetary Authority of Singapore exchange rate as of 20th January 2025: US$1=S$1.2852. Figures were rounded to the nearest dollar.

workflows. Throughout the course of SCINTIX treatment, responders will be experiencing tumour shrinkage, which can decrease the efficacy of the FDG in highlighting the treatment target. Thus, some cases may require re-planning to ensure the biological signal remains sufficiently able to track the tumour and maximise the clinical benefit.[40]

SCINTIX further distinguishes itself through a multi-target capability that treats FDG-avid and inactive lesions in the same session. Yet the clinical utility of this feature must be balanced against the added layer of complexity it introduces to existing dosimetric planning and quality assurance workflows.[41]

Apart from changes in workflows, the implementation of SCINTIX warrants staff training with the technology itself. Past users expressed interest in a staff training program and dedicated change management strategies for overcoming the learning curve.[39] Without these, the reported complex manual nature of the workflow and a perceived lack of automated image-matching tools hindered clinician acceptability (75% of radiation therapists reporting dissatisfaction).[39]

IX. Concurrent Developments

The landscape of radiotherapy is evolving to address the clinical challenge of intrafractional motion (Table 5). While SCINTIX is currently the only platform that uses real-time biological emissions to direct the beam in relation to the tumour position, the Elekta Unity uses high-field magnetic resonance imaging (MRI) for real-time anatomical gating while utilising biological biomarkers solely to adjust dose strategy for subsequent sessions (inter-fractionally). Similarly, the CyberKnife Synchrony system tracks the tumour in real-time using a robotic arm; however, it relies on anatomical surrogates (gold markers) rather than a direct biological signal.

Table 5 Concurrent development of Adaptive Radiotherapy Technologies for lung and bone cancer

Technology (Manufacturer)	Features	Brief description	Status
CyberKnife Synchrony system (Accuray, Inc.)[30]	Real-time Robotic Tracking	Uses a 6-axis robotic arm to physically move the radiation source with the patient's breathing. Relies on a mathematical model that correlates external chest markers with internal X-ray snapshots of fiducials implanted in the tumour.	Commercially available in Singapore[a], HSA registered
Elekta Unity (Elekta AB)[42]	Real-time Anatomical Tracking & Gating	Uses MRI to re-plan for daily anatomical changes before treatment begins. During the session, it can only gate/pause the beam if the anatomical target moves; it does not change dose intensity or track biology in real-time. Biological biomarkers (DWI) are used solely to assess response and adjust dose strategy for subsequent sessions.	Commercially available in the United States; CE marked

Notes:

[a] No CyberKnife Synchrony System is currently available in public healthcare institutes (Personal communication: Radiation Oncologist from NCIS, February 2026)

Abbreviations: CE, Conformité Européenne; DWI, diffusion-weighted imaging; HSA, Health Sciences Authority; MRI, magnetic resonance imaging;

X. Additional Information

Local clinical experts noted that current SBRT techniques (using ITV or gating) already provide good local control for many patients in Singapore with lung or bone cancer, suggesting that the added complexity of SCINTIX may not be justified for all patients (Personal communication: Radiation Oncologists from NCIS, December 2025 and February 2026). Furthermore, the current technical requirement for a high SUV_{max} threshold (>6.0) may limit the eligibility of the technology to a specific subgroup of highly avid tumours, limiting the size of the patient population where SCINTIX could be useful (Personal communication: Radiation Oncologist from NCIS, December 2025). Clinician also shared concerns about the implementation challenges of the technology, including higher costs, longer treatment times and the need for close coordination with other departments, especially the nuclear medicine department (Personal coordination: Radiation Oncologist from NCIS, February 2026).

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Appendix

Appendix A: Studies included and study design

Table A1. List of included studies

Type of Study	Key evidence base	Supplementary evidence base
Published studies / Abstracts	4	14

Note:

1. Inclusion criteria:
    a. Studies that fulfil the PICO criteria listed in Table 1 (BgRT intervention for lung/bone tumours).
    b. Human clinical studies (Key evidence) and technical/phantom validation studies (Supplementary evidence) supporting regulatory clearance.
2. Exclusion criteria:
    a. Studies evaluating only standard radiotherapy without biology-guidance.
    b. Studies involving non-approved tracers (e.g., PSMA, FAPI) or populations (e.g., prostate cancer).
    c. Duplicate records.

See PRISMA flow diagram for full attrition details.

Table A2. Design and characteristics of included studies

Study	N	Study design	Population	Comparator	Reference Standard	Outcome reported
Vitzthum et al. (2024)[19]	17	Prospective Phase I Trial (BIOGUIDE-X)	Patients with FDG-avid lung/bone tumours	Emulated delivery (vs. Plan)	Approved BgRT Plan	Safety, Technical feasibility (gamma pass rate)
FDA De Novo Summary (DEN220014)[16]	17	Prospective Phase I Trial (BIOGUIDE-X)	Patients with FDG-avid lung/bone tumours	Emulated delivery (vs. Plan)	Approved BgRT Plan	Safety, Technical feasibility (gamma pass rate)
Dan et al. (2025)[20]	45	Prospective Observational Registry (PREMIER)	Patients with lung/bone tumours treated with BgRT	None (Single-arm)	NA	Clinical effectiveness (Local control), Toxicity
Wang et al. (2025)[21]	10	Prospective Case Series	Patients with painful osseous metastases	None (Single-arm)	NA	Symptomatic relief (Pain score), Metabolic response

Note:

Abbreviations: BgRT, biology-guided radiotherapy; FDA, U.S. Food and Drug Administration; FDG, fluorodeoxyglucose; N, number of participants; NA, not applicable; PET, positron emission tomography.

Table A3. Design and characteristics of Supplementary Evidence (Technical/Dosimetric)

Study	N	Study design	Population	Comparator	Reference Standard	Outcome reported
Han et al. (2025)[43]	12	Prospective Observational Study	Patients with lung/bone tumours	None	NA	Intra-fraction PET metric stability
Liang et al. (2019)[23]	6	Retrospective Dosimetric Study	Lung cancer patients (Pre-treatment PET)	Standard ITV-based SBRT	NA	PTV volume reduction, OAR sparing
Pham et al. (2025)[25]	16	Retrospective Dosimetric Study	Patients with lung/bone tumours	Standard C-arm Linac IGRT-SBRT	NA	PTV [50]size, Conformity Index (CI), OAR dose
Surucu et al. (2023)[38]	9	Prospective Workflow Study (Time-Motion)	Patients in BIOGUIDE-X trial	None	NA	Workflow timings (Injection-to-scan, Beam delivery)
Shi et al. (2024)[39]	78	Retrospective Operational Study	Patients treated on RefleXion X1 (IMRT/SBRT)	None	NA	Machine uptime, Reliability, Staff satisfaction
Schmitz et al. (2025)[44]	29	Retrospective Database Analysis	Staging PET/CTs of NSCLC patients	None	NA	Percentage of patients eligible for BgRT

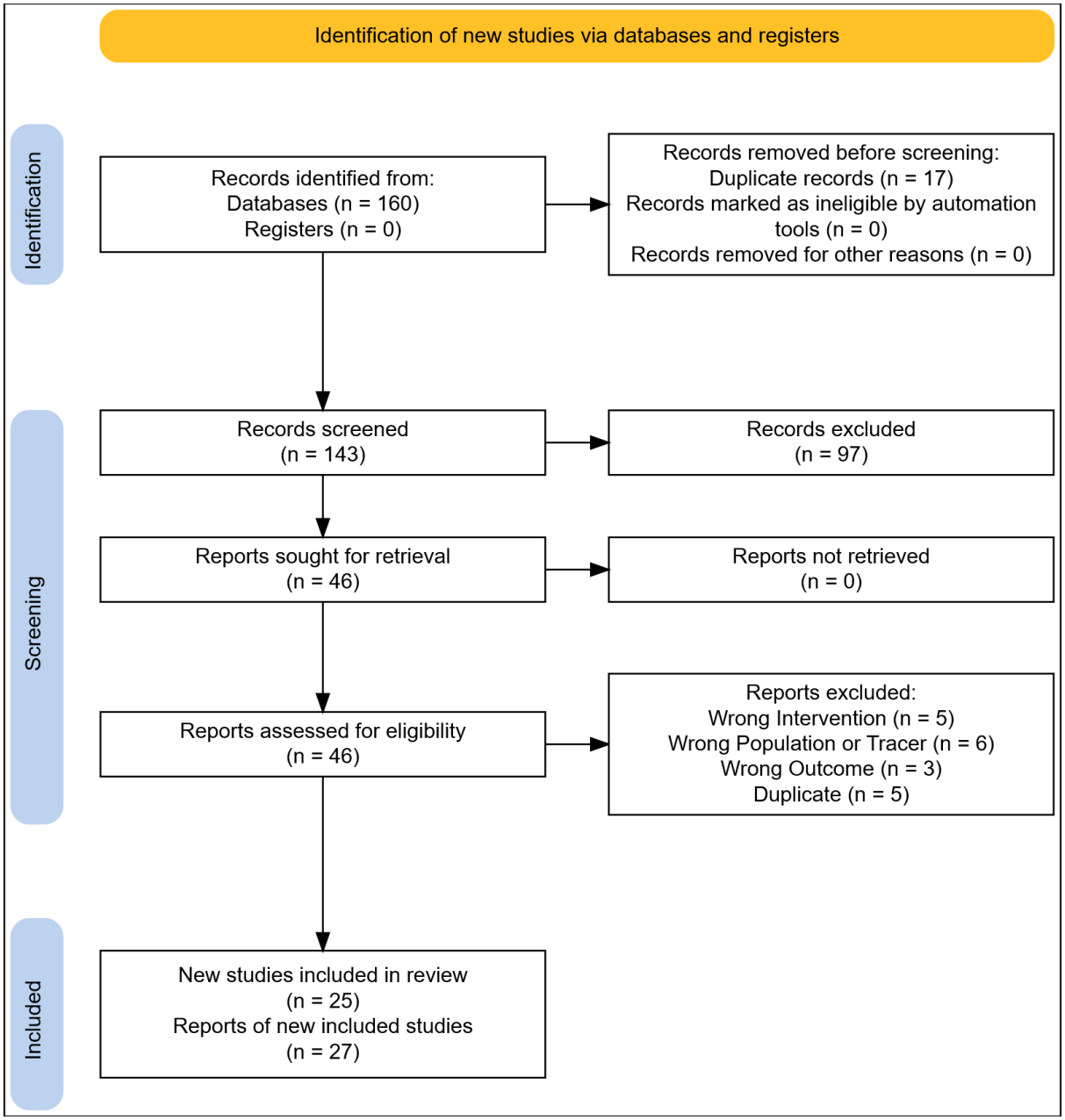
Abbreviations: BgRT, biology-guided radiotherapy; CI, conformity index; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; ITV, internal target volume; N, number of participants; NA, not applicable; NSCLC, non-small-cell lung cancer; OAR, organ at risk; PET, positron emission tomography; PET/CT, positron emission tomography/computed tomography; PTV, planning target volume; SBRT, stereotactic body radiotherapy .

Table A4. Design and characteristics of Supplementary Evidence (Phantom Studies)

Study	Population	Comparator	Outcome reported
Narayanan et al. (2021)[33]	Moving target phantom	Film Dosimetry	Motion tracking accuracy, Dose coverage
Mazin et al. (2012)[26]	Moving/Static phantoms	Film Dosimetry	Margin loss, Dosimetric coverage
Groll et al. (2023)[28]	Phantom with decaying isotope	ArcCHECK	Dose delivery accuracy vs. Signal decay
Bal et al. (2023)[29]	Anthropomorphic lung phantom	Ion Chamber / Film	Intrafraction dosimetric reproducibility
Sharma et al. (2025)[27]	Large spherical targets (40-60 mm)	ArcCHECK / Film	Dosimetric agreement for large targets

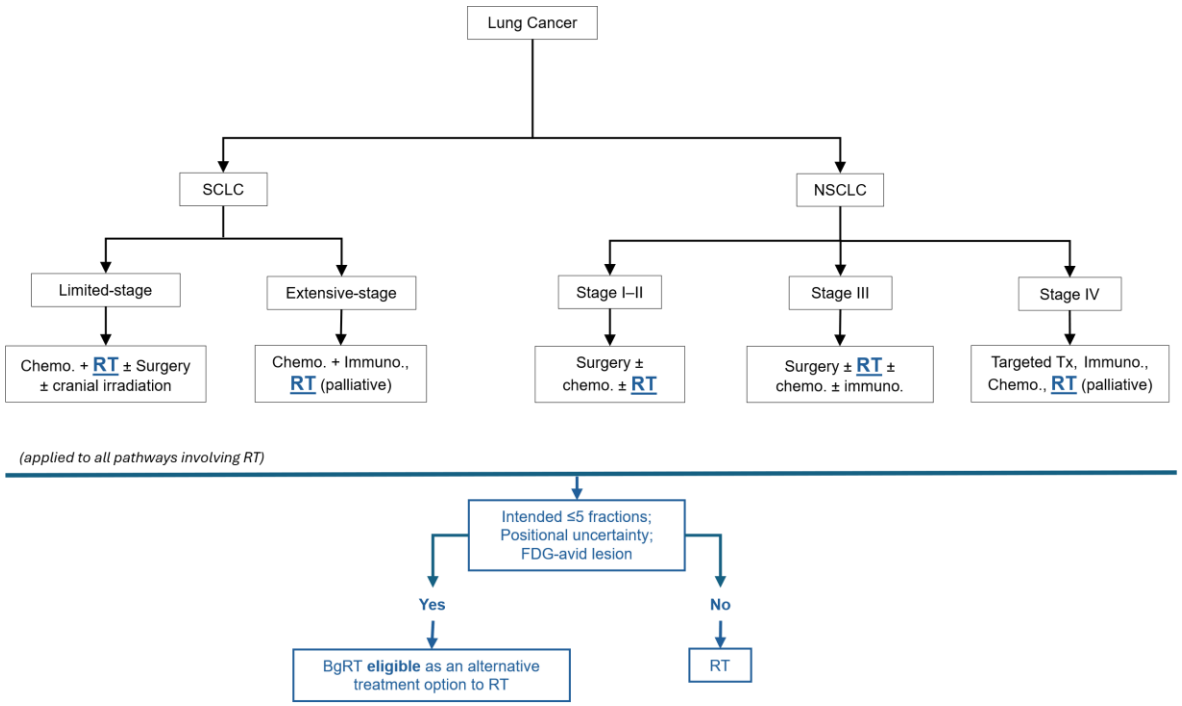
Yang et al. (2014)[30]	Digital Phantom / Patient Breathing Traces	Ground Truth Position	Algorithm tracking error (<2 mm)
Surucu et al. (2024)[32]	Phantoms (Static & Dynamic)	Ion Chamber / Film	System accuracy, Static/Dynamic delivery validation
Fan et al. (2013)[31]	4D Digital Patient Model	Monte Carlo Dose	Dose escalation feasibility
Abbreviations: 4D, four-dimensional; mm, millimetres.			

Figure A1. PRISMA Flow Diagram



Appendix B: Clinical pathways

Figure B1. Clinical pathway according to NCCN Guidance for Lung Cancer

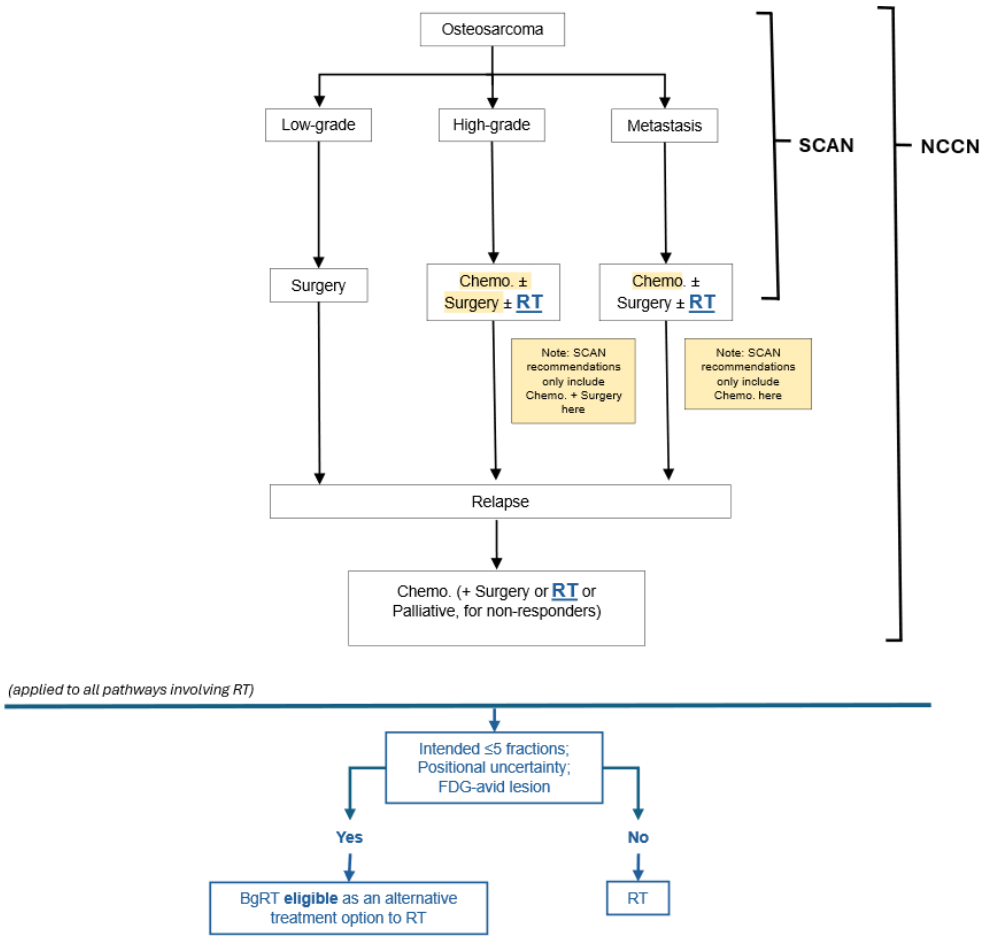


Notes: Multiple international clinical guidelines were reviewed (NSCLC NCCN, NCCN SCLC, ESMO, SingHealth, SCAN) and no high-level differences in treatment pathways were identified. NCCN was therefore selected as the primary reference for the treatment algorithm diagram, both for its greater level of detail and because it is the most widely cited guideline by Singapore Cancer Societies.

Sources: Developed based on NSCLC NCCN, NCCN SCLC

Abbreviations: BgRT, biology-guided radiotherapy (SCINTIX); Chemo., chemotherapy; FDG, fluorodeoxyglucose (18F); Immuno., immunotherapy; NSCLC, non-small cell lung cancer; RT, radiotherapy; SCLC, small cell lung cancer

Figure B2. Clinical pathway according to NCCN Guidance for Osteosarcoma

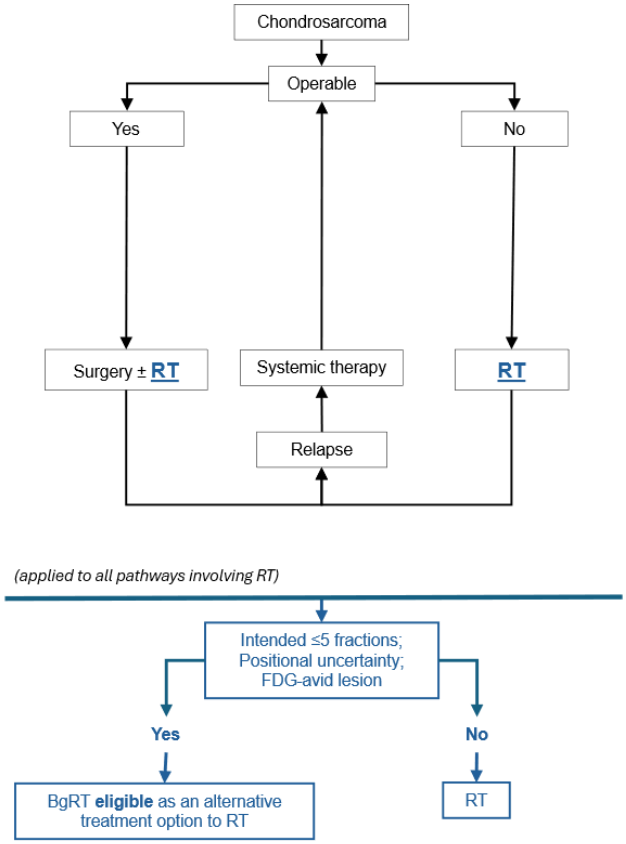


Notes: Multiple international clinical guidelines were reviewed (NCCN, SCAN) and no high-level differences in treatment pathways were identified. NCCN was therefore selected as the primary reference for the treatment algorithm diagram, both for its greater level of detail and because it is the most widely cited guideline by Singapore cancer societies. Other international guidelines (e.g., European, UK, Canadian, Australian) offer recommendations that are slightly different from those illustrated. Scope of SCAN vs NCCN: For metastatic osteosarcoma, SCAN does not specify recommendations for surgery or radiotherapy and does not address post-relapse treatment selection. NCCN provides additional detail for high-grade osteosarcoma, including subgroups for whom RT may be considered, and outlines treatment options after relapse. Apparent differences generally reflect NCCN's greater level of detail rather than conflicting guidance. BgRT eligibility: Wherever RT is shown, BgRT may be considered as an alternative to other RT if eligibility criteria are met: intended ≤5 fractions, acceptable positional uncertainty, and an FDG-avid target lesion (consistent with current FDA clearance).

Sources: Developed based on NCCN

Abbreviations: BgRT, biology-guided radiotherapy (SCINTIX); Chemo., chemotherapy; FDG, fluorodeoxyglucose (18F); Immuno., immunotherapy; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; SCAN, Singapore Cancer Network

Figure B3. Clinical pathway according to NCCN Guidance for Chondrosarcoma



Notes: Multiple international clinical guidelines were reviewed (NCCN, ESMO, SCAN) and no high-level differences in treatment pathways were identified. NCCN was therefore selected as the primary reference for the treatment algorithm diagram, both for its greater level of detail and because it is the most widely cited guideline by Singapore cancer societies.

Sources: Developed based on NCCN

Abbreviations: BgRT, biology-guided radiotherapy (SCINTIX);; FDG, fluorodeoxyglucose (18F); RT, radiotherapy

Appendix C: Detailed procedure-related outcomes

Technical performance

Using standard SBRT planning techniques as the comparator, SCINTIX demonstrated superior dosimetric accuracy.

Table C1. Technical and Dosimetric Accuracy of SCINTIX

Study	Outcomes	Comparison	Result
Liang et al. (2019)[23]	PTV Volume Reduction Organ at Risk Sparing	BgRT vs. ITV-SBRT (Lung)	21.5% reduction Lung V20Gy reduced by 4.4%
Pham et al. (2025)[25]	PTV Volume Reduction	BgRT vs. IGRT-SBRT (Lung)	32.3% reduction (24.5 cc vs 36.2 cc)
Vitzthum et al. (2024)[19]	Delivery Feasibility	BgRT vs. Planned Dose	94.1% of fractions achieved accurate dose delivery
Narayanan et al. (2021)[33]	Tracking Accuracy (Phantom)	BgRT vs. Motion	Successful dose coverage of moving target (<3mm margin loss)

Abbreviations: BgRT, biology-guided radiotherapy; cc, cubic centimetres; Gy, Gray; IGRT, image-guided radiotherapy; ITV, internal target volume; mm, millimetres; PTV, planning target volume; SBRT, stereotactic body radiotherapy; V20Gy, percentage of lung volume receiving ≥20 Gy .