RESEARCH PAPER

Radiotherapeutic Optimization for Oligometastases in Breast and Lung Cancer: A Comparative Review of Global and Kazakhstani Clinical Strategies

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ABSTRACT

Oligometastatic disease, first outlined by Hellman and Weichselbaum in 1995, describes a limited metastatic state in which the number and volume of secondary deposits are small enough to allow local ablative therapy with curative or sustained disease-control intent. Over the last decade, stereotactic ablative radiotherapy (SABR), stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have moved from an experimental niche into mainstream oncology, driven by randomized evidence from SABR-COMET, the Gomez and Iyengar phase 2 trials in NSCLC, ORIOLE in prostate cancer, and several breast-specific analyses. This review synthesizes the current technical and clinical evidence on radiotherapy optimization for oligometastases arising from breast (ICD-10 C50) and lung (ICD-10 C34) primaries, with specific attention to stage IV disease and to the workflow modifications required when ablative radiotherapy is layered onto modern systemic therapy. We compare diagnostic pathways, fractionation schemes, immobilization methods and toxicity profiles used in major international centers with current capabilities and emerging practice at the Kazakh Institute of Oncology and Radiology (KazIOR) in Almaty. Published data support a 2 to 5 year overall survival benefit when SABR is added to standard of care for up to five metastases, with grade 3 or higher toxicity in approximately 4 to 18 percent of patients depending on anatomical site. Local control rates consistently exceed 80 percent at 2 years for pulmonary, osseous and hepatic targets. The Kazakhstani experience remains in an early consolidation phase; targeted investment in image-guided delivery platforms, 4D-CT simulation and MR-based planning can narrow the gap between Almaty and European reference centers within a short timeframe. Barriers remain: heterogeneous definitions of oligometastasis, uneven access to PET-CT and diagnostic MRI, and very limited prospective Kazakhstani outcome data. The next five years should be spent on structured registries, harmonized fractionation protocols for bone, lung and brain targets, and careful integration of SABR with immune-checkpoint therapy where tumor biology supports it.

Keywords: oligometastasis; stereotactic body radiotherapy; SBRT; SABR-COMET; stereotactic radiosurgery; breast cancer metastases; lung cancer metastases; radiation oncology; Kazakhstan; KazIOR; palliative radiotherapy; local consolidative therapy; stage IV cancer.

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1. INTRODUCTION

Breast and lung tumors are the two largest contributors to the global cancer burden. The most recent Globocan figures estimate roughly 2.3 million new breast cancer cases and 2.2 million new lung cancer cases each year, together accounting for about one in four of all oncologic diagnoses worldwide [1]. Lung cancer remains the leading cause of cancer mortality; breast cancer is the fifth. Kazakhstan reproduces this pattern. National statistics compiled by Kaidarova and colleagues report 5,021 new breast cancer cases and 3,615 new lung cancer cases in 2021, corresponding to the first and third positions in the overall incidence ranking, and 2,086 lung and 1,195 breast cancer deaths for the same year [2].

A sizeable fraction of these patients presents with, or later develop, distant spread. For many decades this event was treated as a uniform terminal state requiring only palliative systemic therapy and symptom-directed radiation. That framing eroded after Hellman and Weichselbaum argued in 1995 that an intermediate clinical category sits between truly localized disease and diffusely disseminated metastatic disease [3]. In this intermediate group the number of secondary sites is small, growth kinetics are indolent, and patients may genuinely benefit from direct local ablation of each deposit.

The idea was controversial at first. It matured slowly through retrospective surgical series of pulmonary and hepatic metastasectomy, then accelerated once linear accelerators became capable of delivering large single-fraction or hypofractionated doses with sub-millimeter positional accuracy. Between 2016 and 2023 the SABR-COMET trial, the Gomez and Iyengar phase 2 studies in NSCLC, ORIOLE in prostate cancer, and breast-focused analyses such as NRG-BR002 reshaped the evidence base [4,5,6,7]. Oligometastatic disease is now formally recognized in NCCN and ESTRO/EORTC consensus documents, with a working definition centered on one to five metachronous or synchronous metastases amenable to radical local therapy [8,9].

Radiation oncology has been a direct beneficiary of this shift. SRS, SRT and SBRT offer an ablative local option with total procedure times of minutes rather than weeks. Biologically effective doses above 100 Gy can be deposited in tumors between 1 and 5 cm while holding organ-at-risk exposure within tolerable ranges [10]. Whether these techniques extend overall survival, whether they delay systemic progression, and which subgroups obtain real benefit, are questions that continue to drive trial design.

Kazakhstan has invested substantially in modern radiotherapy infrastructure over the last decade. KazIOR, based in Almaty, operates image-guided linear accelerators and maintains a dedicated stereotactic program. The national cancer registry is functional, PET-CT capacity is expanding, and an MRI-Linac installation is under discussion at the national level. Even so, geographic access is uneven across a country of 2.7 million square kilometers, multidisciplinary protocols for oligometastatic disease are not harmonized between regional oncology dispansaries, and published outcome data from Kazakhstani cohorts remain sparse. Addressing that gap is the broader motivation behind this review and the doctoral research it accompanies.

This article has three aims. First, we summarize the biological and clinical rationale for treating oligometastases with modern radiation techniques, drawing on the randomized evidence base. Second, we compare technical delivery workflows, fractionation regimens and toxicity profiles used in international reference centers against current practice in Kazakhstan, with a focus on C50 and C34 primaries. Third, we discuss how optimization can proceed at KazIOR and similar centers, including quality-of-life assessment, fractionation selection for painful bone disease, and integration with contemporary systemic therapy in stage IV settings.

2. MATERIALS AND METHODS OF THE REVIEW

This is a narrative review prepared in accordance with SANRA guidance for non-systematic reviews. We searched PubMed, Embase and the Cochrane CENTRAL database from January 1995 to December 2025 using combinations of the terms oligometastasis, oligometastatic, oligoprogression, stereotactic body radiotherapy, SBRT, SABR, stereotactic radiosurgery, breast cancer, non-small cell lung cancer, NSCLC, bone metastases and brain metastases. We also screened the reference lists of the NCCN Guidelines (Central Nervous System Cancers; Breast Cancer; NSCLC; Bone Cancer) and of the ESTRO-EORTC OMEC consensus documents. Priority was given to randomized controlled trials, prospective phase 2 studies, consensus guidelines and large registry analyses. Kazakhstan-specific material was retrieved from the

annual reports of the Republican Oncology Service and from internal KazIOR dosimetric databases referenced by institutional permission. We did not attempt a meta-analytic pooling of effect sizes; this would exceed both the review's scope and the comparability of the underlying studies, which use different definitions of oligometastasis and different response assessment tools.

3. OLIGOMETASTATIC DISEASE: BIOLOGY AND OPERATIONAL DEFINITIONS

Hellman and Weichselbaum proposed oligometastasis as a conceptually distinct stage of the metastatic cascade, not merely a statistical description of low metastatic burden [3]. In their model the spreading cancer cell population has not yet acquired the full phenotype necessary for widespread seeding and growth, so eliminating the few overt deposits may translate into prolonged disease control or even cure in selected patients. The model has since been refined with molecular data. Lussier and colleagues described a microRNA signature that discriminates oligometastatic from polymetastatic phenotypes in NSCLC, and Uppal and co-workers showed that primary tumors giving rise to oligometastatic disease have distinct transcriptomic profiles [11,12]. These biological arguments are imperfect but they are more than hand-waving: they explain why patient selection matters so much and why simply counting lesions is not enough.

The operational definition that has emerged from the ESTRO/EORTC OMEC-2 consensus recognizes five clinically relevant states: genuine oligometastatic disease (1 to 5 metastases at diagnosis or relapse without prior polymetastatic history), oligorecurrent disease (after a disease-free interval), oligoprogression (progression at a limited number of sites during otherwise controlled systemic disease), oligopersistence (limited residual active disease after systemic therapy) and induced oligometastasis (polymetastatic disease reduced to five or fewer sites by systemic therapy) [9]. Each state has different implications for prognosis and for the expected benefit of local ablative treatment. In most randomized trials the upper bound has been five metastases, although SABR-COMET-10 and NRG-BR002 extended the cap to ten lesions in selected scenarios.

For day-to-day practice at a center like KazIOR, three practical questions determine whether a patient is a candidate for an oligometastasis-directed radiotherapy strategy. First, has systemic disease been appropriately excluded or characterized by high-quality imaging, ideally whole-body PET-CT plus brain MRI? Second, is the primary tumor controlled, or is effective control planned in parallel? Third, is life expectancy long enough (generally over six months) to make an ablative investment worthwhile? Patients who cannot meet these conditions are better served by conventional palliative radiotherapy schedules directed at symptomatic sites.

4. DIAGNOSTIC WORKUP FOR OLIGOMETASTATIC DISEASE

Accurate staging is the single most important prerequisite for oligometastasis-directed radiotherapy. Under-staging converts what looks like oligometastatic disease into a clinically silent polymetastatic situation in which aggressive local therapy wastes resources and delays effective systemic therapy. Over-staging, in the opposite direction, denies ablative treatment to patients who could still benefit.

4.1 PET-CT with 18F-FDG

Whole-body 18F-FDG PET-CT has become the imaging workhorse for oligometastatic workup in lung and extracranial breast cancer disease. Compared with standalone contrast-enhanced CT, it increases the detection rate of occult distant disease by approximately 10 to 15 percentage points in NSCLC and by 5 to 10 percentage points in breast cancer staging beyond clinical stage IIB [13,14]. Standard uptake value (SUV) thresholds are less useful than morphology and interval change; nonetheless an SUVmax above 2.5 in a new lesion usually merits tissue sampling or close interval follow-up.

In Kazakhstan, PET-CT capacity has expanded notably since 2017, with scanners operating in Almaty, Astana and Shymkent. Access is nonetheless uneven for patients in oblast-level dispansaries, where whole-body diagnostic CT and bone scintigraphy remain the default. Routing patients into the KazIOR PET-CT workflow before committing to a stereotactic course is a reasonable minimum standard for oligometastatic candidates, even when this requires interregional travel.

4.2 MRI for brain and spine

Contrast-enhanced brain MRI is mandatory before SRS planning and strongly recommended at baseline for any lung cancer patient considered for an oligometastatic pathway, as up to 25 percent of patients with NSCLC and suspected limited disease harbor occult brain metastases [15]. Volumetric T1 post-gadolinium sequences are preferred for target delineation; modern SRS planning additionally benefits from MP-RAGE or SPACE sequences with 1 mm isotropic voxel size. For spinal disease, contrast-enhanced MRI with T1 and STIR sequences is the reference for SBRT target definition, especially when epidural extension is suspected.

4.3 Response assessment

The research community has not fully converged on a single response framework for oligometastasis-directed SABR. WHO and RECIST 1.1 remain the default for most clinical trials, but neither handles the problem of radiation-induced changes around treated volumes particularly well. PERCIST has been used in PET-based protocols. For pulmonary targets, radiation-induced fibrosis often mimics progression on CT and can trigger inappropriate second-line therapy unless corrected by PET or by careful temporal follow-up. PERFECT criteria, proposed by the Dutch cooperative group, attempt to correct this problem but are not yet widely adopted [16].

5. RADIOTHERAPY TECHNIQUES: CONVENTIONAL AND STEREOTACTIC APPROACHES

5.1 Conventional fractionated radiotherapy and IMRT

Conventional fractionated external beam radiotherapy (CFRT) and intensity-modulated radiotherapy (IMRT) remain the fallback options in many settings, and not only in low-resource centers. For oligometastatic bone disease with broad, painful osseous involvement and limited survival expectancy, a single 8 Gy fraction or 20 Gy in 5 fractions delivers equivalent pain relief to more complex schedules with less toxicity [17,18]. This is an important point often lost in the enthusiasm around SBRT: not every metastasis needs an ablative dose. About 60 to 70 percent of patients obtain meaningful pain relief within four weeks of a single 8 Gy fraction, and retreatment can be safely given if symptoms recur.

IMRT adds value when conventional doses would overlap with critical organs at risk, especially for paraspinal, pelvic or head-and-neck-adjacent disease. Its dosimetric advantages over three-dimensional conformal radiotherapy (3D-CRT) are most pronounced in re-irradiation scenarios and in patients with complex anatomy. In the current Kazakh clinical workflow, CFRT and IMRT account for the majority of palliative treatments delivered to C50 and C34 patients with distant disease, reflecting available equipment and training rather than a deliberate preference for conventional dose.

5.2 Stereotactic radiosurgery (SRS)

SRS delivers a single large dose, typically 15 to 24 Gy, to intracranial targets with a diameter generally below 3 cm. The technique was developed by Leksell in the 1950s using the Gamma Knife unit; it is now routinely performed on dedicated Gamma Knife, CyberKnife and conventional linear accelerator platforms fitted with micro-multileaf collimators and frameless immobilization. Modern linac-based SRS achieves submillimeter accuracy through cone-beam CT image guidance and six-degree-of-freedom couches, with a planning workflow that can be completed in a single day [19].

For brain metastases SRS has largely displaced whole-brain radiotherapy (WBRT) as the first-line approach in patients with up to four lesions, and data from the JLGK0901 prospective Japanese study extended this indication to ten lesions without loss of overall survival [20]. The NCCTG N0574/Alliance trial demonstrated that adding WBRT to SRS does not improve survival and accelerates cognitive decline, a finding that transformed practice in Europe and North America and that is now broadly accepted in Kazakhstan [21]. Typical prescription doses range from 24 Gy for lesions below 2 cm, 18 Gy for 2 to 3 cm targets, and 15 Gy for larger lesions up to 4 cm, with a strong relationship between dose and local control at the margin of feasibility [22].

5.3 Stereotactic radiotherapy (SRT) and hypofractionated SRS

For intracranial targets exceeding 3 cm, or abutting critical structures such as the brainstem and optic apparatus, single-fraction SRS carries an unacceptable risk of radionecrosis. Hypofractionated stereotactic radiotherapy (HS-SRT), typically 27 Gy in 3 fractions or 30 Gy in 5 fractions, achieves comparable local control with a markedly lower rate

of symptomatic radionecrosis. A prospective multicenter series by Minniti and colleagues reported 1-year local control above 90 percent and a radionecrosis rate below 8 percent for HS-SRT in lesions above 2 cm, compared to 15 to 25 percent after single-fraction SRS at the same size range [23].

5.4 Stereotactic body radiotherapy (SBRT/SABR)

SBRT (the international term SABR is used interchangeably) delivers 30 to 60 Gy in 1 to 8 fractions to extracranial targets using image guidance, custom immobilization, and tight planning target margins derived from 4D-CT simulation when respiratory motion is relevant. For peripheral pulmonary metastases, schedules such as 54 Gy in 3 fractions, 48 Gy in 4 fractions, or 50 Gy in 5 fractions are typical, delivering biologically effective doses (BED) above 100 Gy assuming an α/β ratio of 10. Central pulmonary targets require de-escalation: the RTOG 0813 dose-finding study established 60 Gy in 5 fractions as the maximum tolerated dose for central lesions, with a 7.2 percent rate of grade 3 or higher pulmonary toxicity [24].

For vertebral metastases, spine SBRT delivers 24 Gy in 2 fractions or 24 Gy in 1 fraction, with the single-fraction schedule validated by the randomized CCTG SC.24 trial against conventional 20 Gy in 5 fractions [25]. Complete pain response at 3 months was 36 percent in the SBRT arm versus 14 percent in the CFRT arm, a clinically meaningful difference that justifies the extra resource investment in suitable patients. Vertebral compression fracture is the most common late toxicity, reported in 5 to 14 percent of patients depending on pre-treatment BMI, osteoporosis status and lesion volume [26].

The technical prerequisites for safe SBRT include 4D-CT or breath-hold simulation for mobile targets, image-guided verification with cone-beam CT or surface imaging before each fraction, and a rigorous peer-review process for target and organ-at-risk delineation. Centers without a dedicated motion management program should not deliver pulmonary or hepatic SBRT; the toxicity consequences of geographic miss in this setting are severe. KazIOR has implemented 4D-CT and deep-inspiration breath hold protocols in the last four years, and cone-beam CT-guided delivery is now standard for all stereotactic cases at the central Almaty facility.

Table 1. Commonly used dose-fractionation schedules for oligometastatic and palliative radiotherapy in breast and lung primary cancer.

Anatomical site	Schedule	BED (α/β=10)	Intent	Reference trial / guideline
Bone, uncomplicated, painful	8 Gy × 1	14.4 Gy	Palliative	Chow 2007 [17]; Lutz 2017 [18]
Bone, weight-bearing, long prognosis	20 Gy / 5 fx	28 Gy	Palliative	Lutz 2017 [18]
Vertebral body, single metastasis	24 Gy × 1 (SBRT)	81.6 Gy	Ablative	CCTG SC.24 [25]
Peripheral lung, 1–3 cm	54 Gy / 3 fx SBRT	151 Gy	Ablative	Nguyen 2019 [27]; NCCN [8]
Central lung, oligometastasis	60 Gy / 5 fx SBRT	132 Gy	Ablative	RTOG 0813 [24]
Brain, single lesion <2 cm	24 Gy × 1 SRS	81.6 Gy	Ablative	RTOG 9005 [22]
Brain, 2–3 cm	18 Gy × 1 SRS	50.4 Gy	Ablative	RTOG 9005 [22]
Brain, 3–4 cm or critical location	27 Gy / 3 fx HS-SRT	51.3 Gy	Ablative	Minniti 2016 [23]

Anatomical site	Schedule	BED (α/β=10)	Intent	Reference trial / guideline
Liver oligometastasis	45 Gy / 3 fx SBRT	112.5 Gy	Ablative	Rusthoven 2009 [28]

6. LANDMARK CLINICAL EVIDENCE FOR ABLATIVE RADIOTHERAPY IN OLIGOMETASTASES

The enthusiasm that the oligometastatic paradigm generated in the early 2010s outstripped its evidence base for many years. The last decade has gone some way to correcting that imbalance, although the available trials remain small, mostly phase 2, and rarely powered for overall survival. Five studies dominate current practice.

6.1 SABR-COMET

The SABR-COMET phase 2 randomized trial enrolled 99 patients with up to five metastases from any primary and a controlled primary tumor, randomizing 2:1 to standard of care with or without SABR to all metastatic sites [4]. Median overall survival was 41 months in the SABR arm versus 28 months in the control arm; 5-year overall survival was 42.3 percent versus 17.7 percent, and progression-free survival improved from 5.4 to 11.6 months [29]. Grade 2 or higher toxicity was higher in the SABR arm (29 versus 9 percent) and three treatment-related deaths were reported, a finding that triggered refinement of quality-assurance requirements in subsequent studies. The follow-on trials SABR-COMET-3 (1 to 3 metastases), SABR-COMET-10 (4 to 10 metastases) and SABR-COMET-PRO (prostate) are still accruing or in early analysis.

6.2 Gomez and Iyengar phase 2 trials in NSCLC

Gomez and colleagues randomized 49 patients with oligometastatic NSCLC (3 or fewer residual metastases after first-line systemic therapy) to local consolidative therapy with surgery or radiotherapy versus maintenance or observation [5]. Progression-free survival was 14.2 months with local consolidation versus 4.4 months without. The trial was stopped early for efficacy. A longer follow-up analysis reported overall survival of 41.2 months versus 17 months in favor of consolidation [30]. Iyengar and co-workers, in a single-institution phase 2 trial, found a similar PFS benefit with SABR-based consolidation (9.7 versus 3.5 months) [6]. The larger NRG-LU002 phase 2/3 trial closed without demonstrating a PFS or OS advantage in the overall intention-to-treat population, a result that tempered some of the enthusiasm generated by the earlier phase 2 studies [31]. The negative NRG-LU002 result is important context: oligometastatic NSCLC is heterogeneous, modern systemic therapy works better than the regimens used in Gomez and Iyengar, and the benefit of local consolidation may be concentrated in biologically selected subgroups.

6.3 ORIOLE and STOMP in prostate

ORIOLE and STOMP, both randomized phase 2 trials in oligometastatic hormone-sensitive prostate cancer, showed that SABR delays the need for androgen deprivation therapy and reduces progression at six months [32,33]. ORIOLE additionally demonstrated that patients with a high-risk ctDNA mutational signature had disproportionate benefit, supporting biological rather than purely anatomical selection.

6.4 NRG-BR002 in breast cancer

NRG-BR002 randomized 125 women with oligometastatic breast cancer (up to four metastases) to standard systemic therapy with or without ablative local therapy (SBRT or surgery) [7]. At a median follow-up of 30 months, there was no difference in progression-free survival or overall survival. This result is the single most important piece of evidence for breast oncologists and radiation oncologists working in C50 oligometastases. It argues strongly against routine, biology-agnostic application of ablative radiotherapy to all breast oligometastases, and suggests that the oligometastatic paradigm in breast cancer may require tighter subgroup definitions (for example, ER-positive, bone-limited disease with long prior disease-free interval) before a benefit can be reliably demonstrated.

It bears repeating: the positive signal from SABR-COMET includes too few breast cancer patients to generalize, and NRG-BR002 is essentially neutral. Oligometastatic breast cancer patients should be enrolled in trials wherever possible, counseled carefully about uncertainty, and offered ablative

radiotherapy in situations where symptom control, delay of systemic therapy change, or treatment of a solitary threatening lesion provides a clear individual rationale.

7. RADIOTHERAPY OPTIMIZATION FOR BREAST CANCER OLIGOMETASTASES (C50)

Breast cancer oligometastases have several distinctive clinical features. The most common sites of spread are bone (roughly 65 to 70 percent of first distant recurrences), liver (20 to 30 percent), lung (15 to 25 percent) and brain (5 to 15 percent, higher in HER2-positive and triple-negative subtypes) [34]. Disease biology is highly subtype-dependent: ER-positive tumors often relapse late with bone-dominant oligometastatic disease, HER2-positive tumors show an elevated brain metastasis rate after control of extracranial disease, and triple-negative tumors behave more aggressively with a narrower therapeutic window for ablative local therapy.

Retrospective data from European and North American centers report 5-year overall survival between 25 and 45 percent for carefully selected patients treated with systemic therapy plus SBRT for oligometastatic breast cancer, compared to 10 to 20 percent for historical series without local ablation [35]. These numbers are attractive but reflect intense selection bias. NRG-BR002 is the only randomized reference point currently available, and as discussed it was neutral.

Within this cautious frame, bone-limited oligometastatic disease is the most defensible indication for SBRT in breast cancer. Single-fraction spine SBRT at 24 Gy achieves durable pain response in around two-thirds of patients at three months, with a five to ten percentage point advantage over conventional 20 Gy in 5 fractions [25]. Non-spine bone oligometastases respond similarly well; a phase 2 randomized study by Nguyen and colleagues at MD Anderson reported 62 percent complete pain response at 6 months with single-fraction SBRT versus 36 percent with multi-fraction conventional radiotherapy [27]. For the breast cancer patient with one or two painful bone deposits, an active primary on endocrine therapy, and a life expectancy beyond 12 months, SBRT is a reasonable option where institutional expertise and platform availability allow.

Brain metastases from breast cancer deserve separate comment. HER2-positive disease responds disproportionately well to SRS and HS-SRT, and the extracranial disease trajectory has been transformed by tucatinib, trastuzumab deruxtecan and neratinib in recent years. Combining SRS with these agents requires careful timing: SRS should ideally be delivered before or during the first 3 to 4 weeks of a new HER2-directed regimen, because radionecrosis rates increase when these agents are given concurrently with large single-fraction doses to lesions above 2.5 cm [36]. KazIOR and national Kazakhstani guidelines have begun to encode this sequencing constraint into the standard breast cancer brain metastasis pathway.

8. RADIOTHERAPY OPTIMIZATION FOR LUNG CANCER OLIGOMETASTASES (C34)

Lung cancer oligometastases are biologically and clinically distinct from the breast cancer scenario. The primary tumor is often still active at the time distant deposits are detected, disease kinetics are typically faster, and the brain is the most common site of initial relapse. Contemporary management integrates systemic therapy (targeted therapy for EGFR, ALK, ROS1 and other driver-mutation positive tumors; immune checkpoint inhibition for PD-L1 high tumors; chemo-immunotherapy elsewhere) with thoracic consolidation and distant ablative radiotherapy where appropriate.

The strongest evidence base for lung-directed local consolidative therapy (LCT) comes from the phase 2 work of Gomez and Iyengar, already discussed, with its supportive individual patient data meta-analysis by Ashworth [37]. That analysis reported a 5-year OS of 29.4 percent in patients receiving aggressive local therapy to the primary tumor and all metastatic sites, compared to 0 percent for those receiving systemic therapy alone, in a cohort of 757 patients with oligometastatic NSCLC. Even accounting for selection bias, the magnitude of separation is striking and has not been explained by systemic therapy advances alone.

When LCT is delivered for an intact primary lung tumor, doses of 60 Gy in 15 fractions or 55 Gy in 20 fractions are typical for medically operable patients declining surgery, while definitive chemoradiation at 60 to 66 Gy in 30 to 33 fractions remains standard for locally advanced scenarios. For distant oligometastatic sites, ablative SBRT is generally preferred. The practical challenge is that oligoprogressive NSCLC (progression at one to three sites while most disease remains controlled on

systemic therapy) frequently requires repeated SBRT rounds, each one shortening the available OAR budget at the treated sites [38]. Without careful cumulative dose tracking and biological dose equivalence calculations the second or third round becomes unsafe.

Small cell lung cancer (SCLC) presents with oligometastatic disease less often; when it does, the biology is usually less favorable and the role of ablative radiotherapy beyond thoracic and intracranial sites is unclear. Most centers, including KazIOR, continue to favor systemic chemotherapy with selective thoracic consolidation and prophylactic cranial irradiation or MRI-based surveillance following the recent MAVERICK and PRIMALung updates.

9. BRAIN METASTASES: OPTIMIZATION WITH SRS AND HIPPOCAMPAL-SPARING TECHNIQUES

Brain metastases occur in 20 to 40 percent of patients with advanced lung and HER2-positive breast cancer, and are a defining complication of stage IV disease. The shift from WBRT-first to SRS-first over the last fifteen years has been one of the most consequential changes in modern radiation oncology. Chang and colleagues at MD Anderson demonstrated that WBRT added to SRS produced a 49 percent rate of cognitive decline at 4 months versus 23 percent with SRS alone [39]. Brown and co-workers confirmed the finding in the larger N0574/Alliance trial, with overall survival equivalent between arms [21].

For patients requiring WBRT, either because of leptomeningeal spread or a miliary pattern unsuitable for SRS, hippocampal-sparing WBRT with memantine improves cognitive preservation. The NRG-CC001 phase 3 trial demonstrated a 26 percent relative reduction in cognitive failure at 6 months with hippocampal avoidance, without compromising intracranial control [40]. Delivery requires IMRT or VMAT planning with strict hippocampal dose constraints ($D100 \leq 9$ Gy, $Dmax \leq 16$ Gy) and carries little additional complexity for centers already delivering head-and-neck IMRT.

The Yamamoto JLGK0901 study is particularly relevant to modern practice. It enrolled 1,194 patients with 1 to 10 brain metastases treated with SRS alone and showed equivalent OS between the 2 to 4 and 5 to 10 metastasis groups [20]. Subsequent analyses have extended this observation to patients with up to 15 metastases in selected scenarios, provided total intracranial tumor volume remains below approximately 15 cm^3. The practical implication is that brain metastasis number should no longer be the primary gatekeeper for SRS eligibility; volumetric burden and performance status matter more.

Dose-fractionation optimization for larger brain metastases was studied in the randomized trial by Minniti and colleagues, which compared single-fraction SRS to 27 Gy in 3 fractions for lesions 2 to 4 cm in diameter. One-year local control was 91 percent in the hypofractionated arm versus 77 percent with single-fraction SRS, and radionecrosis dropped from 22 to 8 percent [23]. This is a clinically meaningful improvement and should be adopted as standard for any brain metastasis above 2 cm.

10. BONE METASTASES: CHOOSING BETWEEN CONVENTIONAL AND ABLATIVE SCHEDULES

Bone metastases are the most common radiotherapy indication in breast cancer patients and the second most common in lung cancer. Most can be treated effectively with conventional hypofractionated regimens: 8 Gy in a single fraction for uncomplicated painful metastases, 20 Gy in 5 fractions for weight-bearing sites with longer expected survival, and 30 Gy in 10 fractions when dose escalation is needed for soft tissue extension [18]. A single 8 Gy fraction achieves pain response in approximately 60 percent of patients, with retreatment needed in around 20 percent within 6 months [17].

Where spine SBRT changes the equation is in three scenarios: oligometastatic disease where durable local control is the goal; radioresistant histologies such as renal cell and melanoma; and previously irradiated vertebral levels requiring re-treatment. The CCTG SC.24 randomized trial directly addressed the first scenario, comparing 24 Gy in 2 fractions of spine SBRT against 20 Gy in 5 fractions of conventional radiotherapy in 229 patients with painful spinal metastases [25]. Complete pain response at 3 months was 35 percent with SBRT versus 14 percent with CFRT, a 21 percentage point absolute difference. Vertebral compression fracture occurred in 11 percent of SBRT patients versus 17 percent with CFRT, against expectations, likely reflecting the better selection criteria and careful dose limits in the SBRT arm.

The Nguyen phase 2 trial at MD Anderson tested single-fraction stereotactic radiotherapy against conventional multi-fraction schedules in predominantly non-spine bone metastases, reporting complete pain response at 6 months of 62 percent with SBRT versus 36 percent with CFRT [27]. These results, consistent with the SC.24 data, are shifting practice guidelines toward SBRT as the default in selected oligometastatic bone disease, provided the center has adequate stereotactic capacity. KazIOR currently delivers spine SBRT on its image-guided linear accelerator with a defined protocol based on international guidelines; caseload is still modest and outcomes should be systematically tracked.

11. OPTIMIZING RADIOTHERAPY IN STAGE IV DISEASE BEYOND THE OLIGOMETASTATIC SUBSET

Not every stage IV patient fits the oligometastatic mold. The majority present with polymetastatic disease in which ablative radiotherapy is biologically implausible and clinically unjustified. In these patients optimization means something different: choosing the shortest, least toxic regimen that achieves symptom control; timing radiotherapy around systemic treatment windows; and avoiding overtreatment of asymptomatic disease. This is where the skills of a radiation oncologist are most undervalued and most needed.

Several practical principles apply. First, for painful bone metastases in polymetastatic stage IV patients, 8 Gy × 1 is usually the correct answer. Higher-dose schedules add toxicity and resource consumption without incremental symptom relief. The Dutch Bone Metastasis Study, the Trans-Tasman study and the Lutz ASTRO evidence-based guideline all converge on this point [18,41]. Second, for symptomatic brain metastases in patients with limited extracranial options, WBRT with hippocampal avoidance and memantine is preferred over SRS when lesion number exceeds 10 to 15 or leptomeningeal involvement is present. Third, for symptomatic bronchial obstruction in lung cancer, 17 Gy in 2 fractions or 20 Gy in 5 fractions delivered endobronchially or externally relieves symptoms in 60 to 70 percent of patients with median durations of 3 to 4 months [42].

The SBRT-versus-CFRT decision for an individual stage IV patient is not a purely technical one; it hinges on expected survival, competing symptoms, and whether the treated lesion is oligoprogressive or merely painful. The ESTRO-ACROP guideline suggests that patients with ECOG performance status of 2 or worse, polymetastatic disease, or life expectancy below three months should generally receive conventional hypofractionated regimens [43]. Patients with oligometastatic or oligoprogressive disease, good performance status and a life expectancy above six months are candidates for ablative SBRT or SRS.

A common source of confusion in local practice is the coding of advanced cancer states. In our institutional audits we occasionally encounter diagnoses listed under generic 'advanced cancer' or 'terminal cancer' codes (sometimes recorded locally as L99 or equivalent catch-all categories), particularly in referrals from regional centers. Clean ICD-10 coding (C34 for lung, C50 for breast, followed by the appropriate M-category modifier to identify the metastatic site) is a precondition for useful audit and outcome research, and should be a basic requirement for any center offering oligometastasis-directed radiotherapy. We are pursuing this upgrade at KazIOR as part of the broader registry development.

12. KAZAKHSTAN IN CONTEXT: EPIDEMIOLOGY, INFRASTRUCTURE AND EMERGING PRACTICE

12.1 Cancer burden and service configuration

Kazakhstan occupies 2.7 million square kilometers, serves a population of roughly 20 million, and operates a tiered oncology service centered on 15 regional oncology dispansaries (in Russian: областные онкологические диспансеры) and three federal institutes, of which KazIOR is the largest and the only accredited national oncology research center. Breast cancer has been the leading female cancer for more than a decade; lung cancer continues to dominate male incidence and overall mortality [2]. The national cancer registry, modernized through the electronic health record platform, provides reasonable coverage of incidence and mortality but is less reliable for treatment patterns, fractionation schedules and late toxicity outcomes.

Radiation therapy services in Kazakhstan have expanded sharply since 2010. The country now operates more than 20 linear accelerators across KazIOR, the regional dispansaries, and a small number of private centers. Modern technology is

concentrated in Almaty, Astana and Shymkent; peripheral centers rely more heavily on older 3D-CRT-capable linacs and cobalt-60 units. Volumetric-modulated arc therapy (VMAT) is available at KazIOR and several regional centers. Dedicated stereotactic programs exist at KazIOR in Almaty and at a small number of secondary sites. A CyberKnife unit was installed in a private Almaty center; Gamma Knife capacity is limited.

12.2 Current practice patterns for oligometastatic radiotherapy

Internal audit data from KazIOR for the 2020 to 2023 period (used as the retrospective cohort for the doctoral work underlying this review) show that palliative radiotherapy for bone metastases was typically delivered as 20 Gy in 5 fractions or 30 Gy in 10 fractions of CFRT, with single 8 Gy fractions used less often than international guidelines would suggest. For brain metastases, WBRT at 30 Gy in 10 fractions was still the predominant approach, with SRS reserved for selected single-lesion cases. For symptomatic lung lesions, 30 Gy in 10 fractions remained common. The SBRT caseload, although growing, was under 40 cases per year across the national system.

These numbers are not a criticism; they reflect the practical reality of scaling modern radiation oncology in a mid-resource setting. They identify three clear opportunities. First, a shift toward single-fraction 8 Gy for uncomplicated painful bone metastases would reduce pressure on treatment slots without compromising pain outcomes, following the Lutz ASTRO guideline. Second, SRS should displace WBRT for patients with one to four brain metastases meeting volumetric criteria, with hippocampal-sparing WBRT reserved for salvage or diffuse scenarios. Third, a structured SBRT program for oligometastatic pulmonary, spinal and hepatic disease, anchored at KazIOR with satellite protocols at regional centers, could be scaled to approximately 150 to 250 cases per year within the current infrastructure.

12.3 Comparison with global reference centers

A comparison between KazIOR's current capabilities and those of European reference centers such as the Erasmus MC in Rotterdam, the Netherlands Cancer Institute in Amsterdam, the Royal Marsden in London, or North American centers such as MD Anderson, Memorial Sloan Kettering and Princess Margaret, is instructive rather than demoralizing. The gap is not in radiobiological understanding or in basic technique; it is in diagnostic imaging throughput, peer-review infrastructure, prospective outcome capture, and clinical trial participation. All four are addressable.

Specific gap-analysis findings include the following. Diagnostic PET-CT throughput per capita in Kazakhstan is roughly 0.4 scans per 1,000 population per year, compared to 2 to 4 scans per 1,000 in Western Europe. National guidance on SABR fractionation is issued but not consistently followed at peripheral centers, where conventional schedules remain dominant. Quality-of-life instruments such as EORTC QLQ-C30, QLQ-BM22 (bone metastases) and QLQ-BR23 (breast cancer) are validated in Russian and Kazakh but are not in routine clinical use; their adoption would immediately improve the evidence quality of any Kazakhstani oligometastasis registry. Radiation oncology peer review is performed at KazIOR but not yet systematically recorded or externally benchmarked.

Table 2. Comparison of capabilities and practice patterns in oligometastasis-directed radiotherapy: Kazakhstan (KazIOR as reference) versus European reference centers (composite of five institutions).

Capability / practice domain	KazIOR / Kazakhstan (2024-2025)	European reference centers
Linac count with IGRT	~20 nationally; all KazIOR linacs IGRT-capable	2-6 per center, 100% IGRT-capable
SBRT programs	Central (KazIOR) + 2-3 satellite; <40 cases/yr	Integrated; 200-800 cases/yr per center
MRI-Linac	Not installed; under national discussion	Installed at most national cancer centers
PET-CT access for staging	Concentrated in Almaty, Astana, Shymkent	Near-universal, <2 week wait
Single-fraction	Available at	Routine

Capability / practice domain	KazIOR / Kazakhstan (2024-2025)	European reference centers
spine SBRT	KazIOR; low case volume	(CCTG SC.24 protocol-aligned)
SRS for 1-10 brain metastases	Available; 1-4 lesions most common indication	Routine up to 10-15 lesions
8 Gy × 1 for painful bone metastasis	Underused; 20 Gy / 5 fx predominates	Default choice per ASTRO guideline
Prospective oligometastasis registry	Not yet implemented	OligoCare (ESTRO) participation
Patient-reported outcome collection	Research-only (Russian-validated instruments)	Routine (EORTC QLQ-C30, QLQ-BM22)
Multidisciplinary tumor boards for SBRT	Implemented at KazIOR; uneven at dispansaries	Mandatory and recorded

Several of the gaps identified in Table 2 are solvable within a single budget cycle. Adoption of the ASTRO and ESTRO guidance on single-fraction bone metastasis treatment requires no capital investment; it only requires adjustment of departmental protocols and peer-review habits. Participation in the European OligoCare registry is open to Kazakhstani centers and would provide immediate quality feedback. Routine quality-of-life data collection using validated Russian and Kazakh-language instruments can be implemented with minimal electronic health record modification. These are the low-hanging items and, in our view, should be the priority for 2026 to 2028.

Capital-intensive upgrades such as MRI-Linac installation, additional PET-CT scanners for the western and northern oblasts, and expansion of CyberKnife capacity belong to a longer planning horizon. The doctoral research program at KazIOR is explicitly designed to generate the outcome data needed to justify this investment, through the prospective collection of safety, local control and quality-of-life data in 60 stereotactically-treated patients over 2023 to 2026, compared against a retrospective cohort of 60 conventionally-treated patients from 2020 to 2023.

13. QUALITY OF LIFE AND TOXICITY OUTCOMES

Most of what patients experience after ablative radiotherapy for oligometastases is not captured by local control rates or overall survival. The EORTC QLQ-C30 global health status score, symptom-specific modules (QLQ-BM22 for bone metastases, QLQ-BR23 for breast cancer, QLQ-LC13 for lung cancer) and brain-specific BN20 questionnaire give a more useful picture. Across published SBRT cohorts, baseline global health status typically sits around 55 to 65 on the 0 to 100 scale, with improvement to 70 to 78 at 3 months in patients who obtain symptom response and no major toxicity [44].

Radiation-specific toxicity patterns by anatomical site are reasonably predictable. For pulmonary SBRT, grade 3 or higher pneumonitis occurs in 2 to 10 percent of patients, rising with central versus peripheral location and with larger V20 values [24]. For spinal SBRT, radiation myelopathy is rare (well under 1 percent) when conventional spinal cord dose constraints are respected; vertebral compression fracture occurs in 5 to 14 percent as noted earlier [26]. For hepatic SBRT, radiation-induced liver disease (RILD) is avoidable with strict mean liver dose constraints (<15 Gy for three-fraction regimens) [28]. For brain SRS, radionecrosis rates depend on volume: 2 to 5 percent for lesions below 2 cm treated at 20 to 24 Gy, rising to 20 percent for lesions above 3 cm treated single-fraction. Hypofractionation mitigates this problem as discussed [23].

Patient experience of ablative radiotherapy is usually better than of conventional fractionation courses, simply because treatment is shorter, transport burden smaller, and pain response faster. In a recent Dutch cohort, patients treated with spine SBRT reported higher pain interference improvement at 4 weeks than those treated with conventional palliative radiotherapy, sustained at 3 months [45]. This finding has practical implications for Kazakhstan: patients living in remote oblasts often face long travel times to regional oncology centers, and shorter course

duration translates directly into fewer clinic visits and lower out-of-pocket cost.

14. FUTURE DIRECTIONS

14.1 Combining SABR with systemic therapy

The combination of SABR with immune checkpoint inhibitors has generated substantial theoretical interest through the putative abscopal effect, in which radiation-induced tumor antigen release augments systemic anti-tumor immunity. Phase 1 and 2 trials have produced mixed results. PEMBRO-RT and MDACC I-SABR suggested increased response rates in NSCLC when SBRT is combined with pembrolizumab, but the benefit has been difficult to reproduce at scale and has not translated into unequivocal OS advantage [46,47]. For oligoprogressive NSCLC on immunotherapy, SBRT to progressing sites while continuing the same checkpoint inhibitor is a clinically sensible strategy but lacks prospective randomized validation.

14.2 Adaptive and MR-guided radiotherapy

MR-Linac platforms deliver radiotherapy under real-time magnetic resonance guidance, allowing adaptive replanning on each treatment day. Early single-arm data suggest that MR-guided SBRT can deliver higher effective biological doses to liver and pancreatic targets with reduced organ-at-risk exposure. Whether the clinical benefit justifies the capital cost is an open question. For Kazakhstan, national-level investment in at least one MR-Linac unit, most logically at KazIOR, would establish a platform for adaptive ablative therapy and support cross-border research collaboration.

14.3 Biomarker-based patient selection

The single most important unresolved question in oligometastatic radiotherapy is who actually benefits. Anatomical definitions alone (one to five lesions) are clinically useful but biologically crude. Circulating tumor DNA, exosome-based miRNA signatures, and multi-omic classifiers are all candidate refinements. The ORIOLE trial showed that ctDNA mutational clusters predict SABR benefit in prostate cancer; analogous signatures for breast and lung oligometastases are in active development [32]. Once validated, these tools will allow the oligometastatic label to be applied to the biology rather than just to the imaging.

14.4 Artificial intelligence in planning and adaptive workflows

Automated organ-at-risk segmentation, AI-assisted target delineation, and machine-learning dose prediction are now mature enough for clinical deployment. In a resource-constrained setting they reduce planning time and homogenize quality across sites that differ in dosimetry experience. KazIOR has piloted deep-learning auto-contouring for thoracic SBRT with reported reductions in planning time of roughly 40 percent. Expansion into vertebral, cranial and abdominal sites is the obvious next step.

15. LIMITATIONS OF THIS REVIEW

This review has several limitations worth stating openly. It is narrative rather than systematic, and we did not use a pre-registered search protocol or formal risk-of-bias assessment. Our emphasis on SABR-COMET, Gomez, Iyengar, ORIOLE and NRG-BR002 reflects our judgment of their importance but inevitably under-weights other studies. Kazakhstani practice data are drawn from KazIOR and should not be uncritically generalized to the full national system. Finally, the evidence base for breast cancer oligometastases is genuinely weaker than for other primary sites, and our cautious interpretation of NRG-BR002 may not be shared by all clinicians.

Public health considerations in oncology patient treatment

Oncology patients constitute a highly vulnerable group from a public health perspective, particularly regarding emerging infectious diseases such as SARS-CoV-2. Chemotherapy-induced immunosuppression markedly increases susceptibility to infections and their complications, necessitating integrated surveillance, infection control, and multidisciplinary management. Curre demonstrates that SARS-CoV-2 infection in cancer patients can result in both acute respiratory illness and post-infectious immune-mediated complications. For example, a documented case involving a patient receiving adjuvant chemotherapy for gastric cancer reported the onset of Guillain–Barré syndrome following COVID-19, likely precipitated by immune dysregulation and cytokine-driven inflammatory responses. These findings underscore the importance of long-term neurological monitoring and prompt identification of autoimmune sequelae in oncology care.

From a broader public health perspective, repurposing antiviral agents with established safety profiles, such as tenofovir-based therapies, provides a strategic advantage for rapidly addressing viral threats in high-risk populations, including cancer patients. In vitro studies indicate that tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) possess significant inhibitory activity against SARS-CoV-2 and demonstrate favorable cytotoxicity profiles, supporting their potential application in therapeutic or prophylactic settings. These strategies are consistent with pandemic preparedness efforts that utilize existing pharmacological resources to reduce morbidity among immunocompromised individuals [48-50].

In summary, public health strategies in oncology should incorporate infection prevention, early identification of atypical and delayed complications, and the judicious use of repurposed therapeutics. Achieving these objectives necessitates coordinated collaboration among oncology, infectious disease, and public health sectors to optimize patient outcomes and minimize risks related to both malignancy and concurrent infections.

16. CONCLUSIONS

Stereotactic ablative radiotherapy has reshaped treatment for selected patients with oligometastatic breast and lung cancer, though the size of the benefit varies by primary site, by biological subtype and by the competing progress of systemic therapy. SABR-COMET provides the strongest phase 2 signal for overall survival benefit; Gomez, Iyengar and Ashworth support a role in oligometastatic NSCLC with the important qualifier that NRG-LU002 failed to extend the finding to the current era of chemo-immunotherapy; NRG-BR002 argues for caution in unselected breast oligometastases; and ORIOLE and STOMP open a biology-first pathway that will likely shape the next decade.

Kazakhstan has built the technical infrastructure for modern oligometastasis-directed radiotherapy but has not yet built the registry, multidisciplinary and quality-of-life measurement scaffolding needed to make that infrastructure productive. The gap with European reference centers is narrower than it looks on paper, and closable with protocol harmonization, single-fraction bone metastasis adoption, expanded SRS for low-volume brain disease, and structured SBRT programs for spine, lung and liver oligometastases. The doctoral research program at KazIOR is designed precisely around these priorities and should generate the first prospective Kazakhstani dataset on stereotactic outcomes in C50 and C34 oligometastases by 2027.

The practical message for Kazakhstani radiation oncology departments is short. Use single-fraction 8 Gy more often for uncomplicated painful bone metastases. Move from WBRT to SRS as the default for one to four brain metastases below 3 cm. Track every SBRT case in a structured registry, with baseline and 3-month QLQ-C30 plus the relevant tumor module. None of this requires new linacs or new buildings; it requires a protocol document, a peer-review habit, and a working spreadsheet.

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ABBREVIATIONS

Abbreviation	Definition
BED	Biologically effective dose
CFRT	Conventional fractionated radiotherapy

Abbreviation	Definition
CBCT	Cone-beam computed tomography
ctDNA	Circulating tumor DNA
EORTC	European Organisation for Research and Treatment of Cancer
ESTRO	European Society for Radiotherapy and Oncology
FDG	18F-fluorodeoxyglucose
HS-SRT	Hypofractionated stereotactic radiotherapy
ICD-10	International Classification of Diseases, 10th revision
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
KazIOR	Kazakh Institute of Oncology and Radiology
LCT	Local consolidative therapy
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
OAR	Organ at risk
OMEC	OligoMetastatic disease classification (ESTRO-EORTC)
OS	Overall survival
PFS	Progression-free survival
PET-CT	Positron emission tomography - computed tomography
PERCIST	PET Response Criteria in Solid Tumors
QLQ-C30	EORTC Quality of Life Questionnaire, Core 30 items
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RILD	Radiation-induced liver disease
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy
SCLC	Small cell lung cancer
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy

Abbreviation	Definition
VCF	Vertebral compression fracture
VMAT	Volumetric-modulated arc therapy
WBRT	Whole-brain radiotherapy
WHO	World Health Organization

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable. This article is a narrative review of published literature and institutional practice descriptions; it does not report primary research on human participants or animals.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

All data cited in this review are available in the public literature referenced above. Aggregate KazIOR practice patterns discussed in Section 12 were derived from internal quality-assurance audits and are available from the corresponding author on reasonable request, within the limits of institutional data-sharing policies.

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CONFLICTS OF INTEREST

None declared.