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Review Article

Optimal timing for local ablative treatment of bone oligometastases in non-small cell lung cancer

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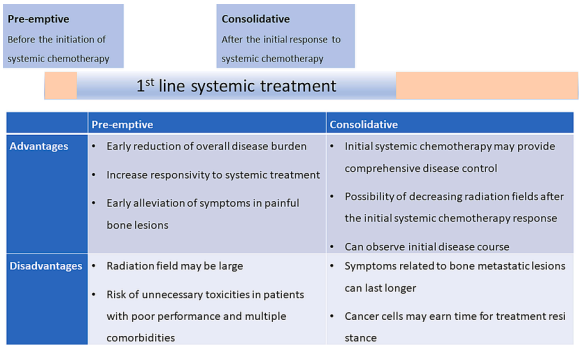
HIGHLIGHTS

- Oligometastases is a transient phase between localized and widespread systemic diseases.
- Bone-only oligometastases are unique in terms of associated symptoms, skeletal-related events and tumor microenvironment.
- Radiotherapy is the most frequently used treatment modality for LAT.
- Decision on timing of LAT should consider potential side effects, and initial responses to systemic treatment.

GRAPHICAL ABSTRACT



	Pre-emptive	Consolidative
Advantages	• Early reduction of overall disease burden • Increase responsivity to systemic treatment • Early alleviation of symptoms in painful bone lesions	• Initial systemic chemotherapy may provide comprehensive disease control • Possibility of decreasing radiation fields after the initial systemic chemotherapy response • Can observe initial disease course
Disadvantages	• Radiation field may be large • Risk of unnecessary toxicities in patients with poor performance and multiple comorbidities	• Symptoms related to bone metastatic lesions can last longer • Cancer cells may earn time for treatment resistance

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ABSTRACT

Oligometastases is a term commonly used to describe a disease state characterized by a limited number of distant metastases, and represents a transient phase between localized and widespread systemic diseases. This subgroup of stage IV cancer has increased in clinical importance due to the possibility of curative rather than palliative treatment. Among advanced lung cancer patients, 30–40% show bone metastases, and can show complications such as pathological fractures.

Many prospective studies have shown efficacy of localized treatment in oligometastatic non-small cell lung cancer (NSCLC) in improving progression-free survival and overall survival. Compared to metastases in other

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organs, bone metastases are unique in terms of tumor microenvironment and clinical outcomes. Radiotherapy is the most frequently used treatment modality for local ablative treatment for both primary and metastatic lesions. Stereotactic body radiation therapy demonstrated more rapid and effective pain control compared to conventional 3D conformal radiotherapy. Radiotherapy improved outcomes in terms of time-to-skeletal related events skeletal-related events (SRE), hospitalization for SRE, pain relief, and overall survival in patients with bone metastases. Decision on timing of local ablative treatment depends on patient's overall clinical status, treatment goals, potential side effects of each approach, and expected initial responses to systemic anti-cancer treatment.

1. Introduction

Among advanced lung cancer patients, 30–40% show bone metastases, with ribs being the most common site of invasion [1,2]. Thirty-five to 40% of lung cancer patients develop bone metastases during the disease course [3]. In general, the median survival of lung cancer patients with bone metastases is less than one year [4,5]. One multicenter study showed that, among individuals with non-small cell lung cancer (NSCLC) and bone metastatic lesions, skeletal-related events occurred in 57.7%, median time until first skeletal-related event was six months, and median survival was 9.5 months [3]. Bone metastases can show complications such as pathological fractures, compression of the spinal cord, pain, and hypercalcemia, and skeletal-related adverse events can severely damage patients' general condition and function [6].

Oligometastases describe a primary tumor with concurrent metastatic lesions and show more indolent features compared to more disseminated metastatic diseases [7]. Studies employ different definitions of oligometastatic disease, but "up to five" and "up to three" metastatic lesions are most common [8]. This subgroup of stage IV cancer has increased in clinical importance due to the possibility of curative rather than palliative treatment.

Many prospective studies have shown efficacy of localized treatment in oligometastatic NSCLC in improving progression-free survival (PFS) and overall survival (OS) [9–14]. Recent trends in prospective studies regarding oligometastatic cancer focus on approaching more specific subgroups of patients in terms of cancer type, disease burden, and distribution of metastatic sites. Compared to metastases in other organs, bone metastases are unique in terms of tumor microenvironment and clinical outcomes. For this reason, the approach to bone oligometastatic diseases in NSCLC is important in view of recent advances in treatment of stage IV NSCLC. In this narrative review, we focused on bone oligometastatic diseases in terms of clinical characteristics and management.

2. Materials and method

2.1. Search strategy

We selected articles, focusing primarily on clinical trials, using the PubMed search engine based on combinations of the following terms: "bone metastasis," "lung cancer," "non-small cell," "limited," "oligometastases," "fracture," "radiotherapy," "surgery," "skeletal," "definitive," "stereotactic," and "curative."

3. Unique tumor microenvironment of bone metastases

Compared to other organs, bone is a relatively immunocompromised area and is an amenable environment in which cancer cells are more likely to proliferate. In the pre-metastatic niche, large numbers of immature and inhibitory immune cells are present, and relatively smaller numbers of T cells and NK cells are present in bone marrow [15,16]. On the other hand, regulatory T-cells (Tregs) account for a large proportion of non-cytotoxic immune cells, and large numbers of other inhibitory cells such as MDSCs are present in bone [17].

Balance between osteoclasts and osteoblasts also is important in the tumor microenvironment. Cancer cells can induce imbalance between osteoblasts and osteoclasts and deter effective bone reconstruction [18]. Lung cancer cells secrete interleukin (IL)-7, and T cell-derived cytokines including receptor activator of nuclear factor-κB ligand (RANKL) and TNF-α are upregulated, further promoting osteoclast production [19]. There are osteolytic and osteogenic bone metastases in lung cancer, while osteolytic metastasis caused by osteoclasts is the predominant type [20]. Osteoclasts can secrete various immunosuppression-inducing substances including indoleamine 2,3-dioxygenase-1 (IDO1) and IL-10. Bone resorption results in the release of TGF-beta, and IL-6 secretion results in T cell differentiation into T helper 17 and Treg cells and further contributes to the formation of an immunosuppressive microenvironment. Th17 lymphocytes release interleukin IL-17 and INF-gamma, and osteoclast differentiation is repeatedly promoted [16].

4. Initial approach to bone oligometastatic diseases

Hellman and Weichselbaum proposed the concept of an oligometastatic state in solid malignancies, which is an intermediate stage between limited and widely disseminated cancer. It was also suggested that the course of this state can be positively affected by systemic and local therapies, including radiation. [7]. The generally accepted definition of oligometastases is the presence of no more than five or no fewer than three metastatic lesions in two organs [21]. Before performing localized treatment to oligometastatic lesions, accurate staging and detection of metastatic lesions are important. Several diagnostic techniques such as PET-CT scan or bone scans are associated with increased survival [16]. Patient symptoms are also important.

Location of bone metastases is one of the highest priority factors to consider for treatment decisions. Whether the metastases are in weight-bearing bones is important because ongoing metastases may involve fractures that would ultimately lead to immobilization. Sites such as the spine and pelvis should be approached with caution, and discussion among multidisciplinary board members including orthopedists and radio-oncologists is essential.

Furthermore, disease burden is important regarding the prognosis of patients with NSCLC and bone metastases. In a retrospective study including 157 NSCLC patients with synchronous single-bone metastatic lesions, metabolic tumor volume (MTV) from PET CT was an independent prognostic factor for cumulative survival. In addition, larger MTV of the bone tended to be related to reduced survival, despite no significant difference [22].

Whether the lesions are symptomatic or painful is also important. Metastases-related pain is ongoing and significantly decreases quality of life. Thus, early localized treatment should be considered for such lesions. Clinicians should also decide whether the lesions are osteolytic or osteoblastic. In many cases, bone metastatic lesions in lung cancer are osteolytic [23]. Imaging such as MRI can be helpful in this situation. A suggested algorithm for managing bone metastases is shown in Fig. 1.

5. Treatment options for definitive therapy

5.1. Radiotherapy

In oligometastatic NSCLC, metastases-directed treatment, such as radiotherapy and resection, significantly improved progression-free survival (PFS) [13,14].

Radiotherapy, the most frequently used treatment modality for local

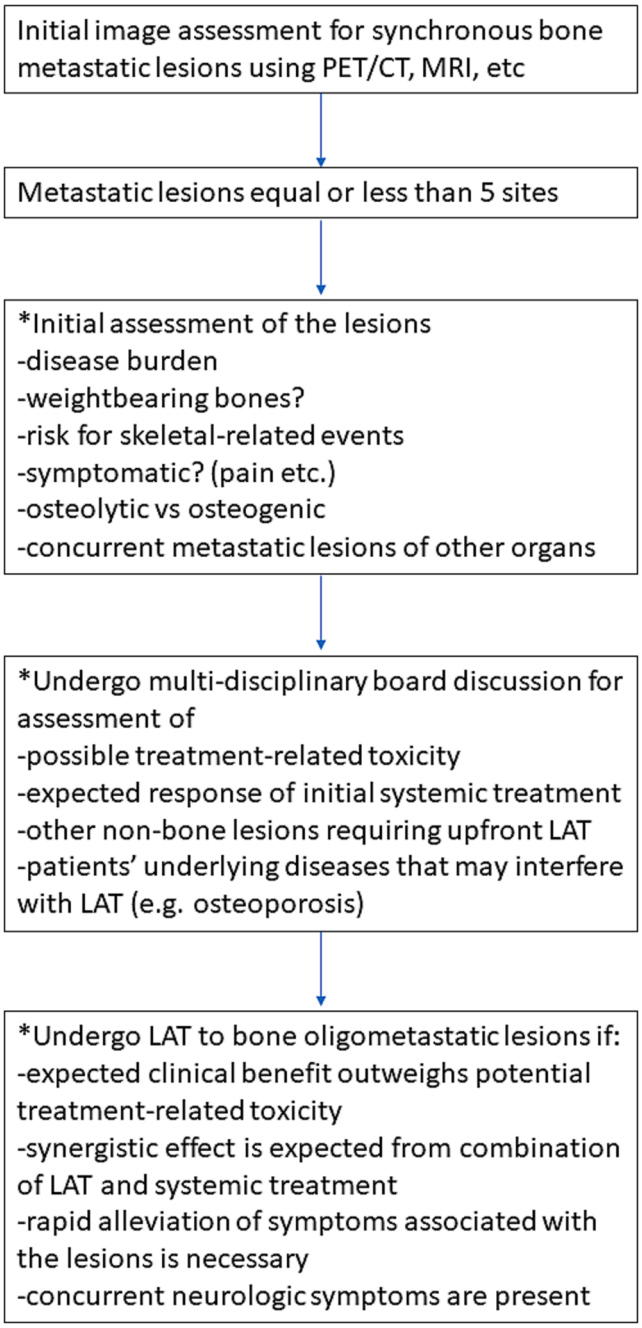

Fig. 1. Suggested algorithm regarding management of bone oligometastses in non-small cell lung cancer. Abbreviation: LAT, local ablative treatment.

ablative treatment (LAT) for both primary and metastatic lesions, has shown remarkable improvement during the last decade, especially in technical aspects. The radiation technique known as stereotactic body radiation therapy (SBRT) can deliver a compact dose of radiological energy to ablate tumor cells of target lesions with steep gradients in all directions, while minimizing collateral damage to normal tissues [24,25]. Several academic societies, including the American Association of Physics in Medicine (AAPM) Task Group 101, the American Society for Therapeutic Radiology and Oncology, and the American College of Radiology (ASTRO and ACR), along with the Canadian Association of Radiation Oncology—Stereotactic Body Radiotherapy (CARO-SBRT) and the National Radiotherapy Implementation Group of the UK, have provided definitions of SBRT as a method of external beam radiotherapy (EBRT) that accurately delivers a high dose of irradiation in one or few treatment fractions to an extracranial target [26–29]. In a randomized trial that evaluated the efficacy of palliative SBRT for metastatic lesions of the spine, SBRT demonstrated more rapid and effective pain control compared to conventional 3D conformal radiotherapy [30]. In another randomized phase 2/3 trial (NCT02163226) in which 49% of the patients were diagnosed with lung cancer, improvement rates for pain were better for single-fraction SBRT than standard multi-fraction radiotherapy in non-spine bone metastases. Furthermore, there was no difference in toxicity between the two radiation techniques [31].

Results of a multicenter randomized phase 2 trial (NCT03523351) were presented in ASTRO 2022. The study aimed to evaluate whether radiation for high-risk bone metastases prevented skeletal-related events (SRE). Total of 78 patients with 122 bone metastases were included and randomized to either prophylactic RT ($n = 39$) or standard of care (SOC) ($n = 39$). Among study patients, the most common primary cancer type was lung (27%), followed by breast and prostate cancer. SRE occurred in only 1.6% of the RT arm compared to 29% of the standard of care arm ($p < 0.001$). The RT arm showed better outcomes in terms of time-to-SRE, hospitalization for SRE, pain relief, and overall survival compared to the SOC arm [32]. Enrollment criteria of the study (more than five lesions) may not overlap with bone oligometastatic diseases, but potential positive effects of prophylactic RT should be accounted for when approaching bone oligometastatic diseases.

Radiotherapy has also shown efficacy in populations with targetable mutations. A retrospective cohort of 131 patients who experienced oligoprogression while on first-line EGFR-tyrosine kinase inhibitors (TKI) showed that local treatment with high-dose irradiation was associated with better overall survival compared to patients who did not receive LAT ($p < 0.0001$). Bone accounted for the largest proportion of sites irradiated [33].

Up until now, no consensus on optimal radiation dose and fractions for local ablative treatment of bone oligometastatic disease have not been definitively reached. In the SABR-COMET trial, a total radiation dose of 35 Gy delivered in 5 fractions was administered to bone metastatic lesions other than femur. For the lesions metastasized to vertebral body, total of 16–20 Gy/1fraction or 30 Gy/3 fractions were administered [9]. From the study conducted by Petty et al., 24 Gy/1 fraction or 27 Gy/3 fractions were administered for the spine lesions. In this prospective, multicenter, phase 2 trial, 27 patients with oligometastatic NSCLC were enrolled. After 3 to 6 cycles of platinum-based chemotherapy, patients who achieved partial response or stable disease underwent consolidative radiation therapy, resulting in a median PFS of 11.2 months (95% confidence interval: 7.6–15.9 months) and median OS of 28.4 months (95% confidence interval: 14.5–45.8 months) [12]. In the study by Sutera et al., a dose of 18–25 Gy/1 fraction was administered to any bone metastatic lesion. The study included lung cancer patients, accounting for 21.8% of the total patients, and the median OS was 26.8 months (95% CI, 8.1–45.4), and median distant PFS was 5.7 months (95% CI, 0.0–11.4) [34]. The studies have employed a high-energy radiation approach to effectively ablate oligometastatic bone lesions.

The number of radiotherapy targets is also an important factor. From recent studies, it is generally advised to consider definitive local therapy for patients who present with a maximum of five distant metastases, as determined through precise imaging modalities. However, it should be taken into consideration that while several prospective trials have included patients with up to five extracranial metastases, the majority of enrolled patients typically had one to two treated oligometastatic lesions [9,14,35,36].

Organs of common metastasis sites of lung cancer other than bone include brain, liver, and adrenal gland [37]. However, specific recommendations regarding concurrent oligometastases to bone and other organs are limited in the current literature. The general principle of managing oligometastases is to consider all lesions, including the primary lung lesion and metastatic lesions, as potential targets for localized treatment, and treatment of all targets is conditionally recommended if

the anticipated clinical benefits outweigh the associated risks [38]. In cases where patients' overall health conditions do not allow simultaneous targeting of all metastatic lesions to bone and other organs, clinicians should decide the sequence of localized treatment based on factors like symptoms associated with the lesions, disease burdens, and expected treatment response from systemic chemotherapy.

5.2. Radiotherapy-related toxicity

Despite advancement in radiation techniques, chances of treatment-related toxicity exist, both acute and late. Acute effects of radiation on bone include inflammation and hematologic suppression [39]. Late or subacute effects occur primarily as increased risk of fracture or insufficiency of bones. Decreased bone density due to radiation may lead to increased likelihood of bone fractures, especially in patients with underlying osteoporosis and osteopenia. Osteoporosis contributes to increased risk of symptomatic fracture, especially of the femur, ribs, and pelvis [39]. Moreover, after radiotherapy, deaths of previously space-occupying tumor cells contribute to destabilization of weight-bearing bones such as the vertebral body, which may lead to increased risk of fractures [40]. In a retrospective study of patients treated with SBRT for non-spine bone metastases, fracture was observed in the treatment volume of lesions in 8.5% of the 106 patients. Lytic lesions and female gender tended to be predictive of fractures [41].

Other than bone toxicity, clinicians should also be aware of toxicity to non-bone tissues. In cases of patients with metastases to bones located near lung parenchyma (e.g., the ribs), irradiation to the lesions may lead to increased chance of pneumonitis when normal lung parenchyma is included in the radiation field. Higher radiation energy may result in an increased chance of treatment-related toxicity [42].

When undergoing radiotherapy to spine metastases, the most critical organ at risk is the spinal cord, which is frequently located adjacent to the target lesion. Radiation myelopathy, which is a fatal complication, may develop if the dose tolerance of the organ is exceeded. Considering that spinal cord damage is often irreversible, careful planning before radiotherapy is essential. It is recommended that an isotoxic dose distribution that does not exceed the dose tolerance of the spinal cord be delivered to minimize possible radiation myelopathy [43]. RT should be considered as priority option if a definitive dose to target metastatic lesion is reachable without exceeding the dose tolerance of normal tissue surrounding the lesion [38].

Radiotherapy-related toxicity can also occur in the esophagus, particularly when performing SBRT to the thoracic spine where the anteriorly located esophagus can be exposed to irradiation. In a retrospective study which included 21 patients under postoperative SBRT to the spine, 3 patients experienced grade 2 esophagitis, and 1 patient had grade 4 esophagitis. [44,45]. However, this study was published more than a decade ago, and due to the advent of advanced radiotherapy techniques, the incidence of radiation-related esophagitis is decreasing.

5.3. Surgery

Several studies have included impact of surgical resection, including vertebrectomy. However, high morbidity can be a problem.

When assessing fracture risks of bones affected by bone metastases, several scoring systems such as Mirels' scoring system for long bones and spinal instability neoplastic score (SINS) classification are available [46]. Both scoring systems consider the site, extent and nature of lesion, as well as the presence of pain. SINS further include alignment and collapse into scoring parameters. Mirels' scoring system is used for long bones [47], while SINS is used for vertebrae [48]. The scoring systems help clinicians accurately assess fracture risks and implement surgical stabilization if necessary.

In a retrospective study including eight patients who underwent partial or total vertebrectomy for lung cancer, 75% of the patients experienced morbidity [49]. Due to the high morbidity related to open surgery, an alternative surgical approach such as minimally invasive spinal surgery (MISS) was attempted in patients with spinal metastases. In a single-institute study of 52 patients who underwent MISS, patients had improvement in neurological status and pain while showing relatively low treatment-related complication rates. In addition, the authors further stated that multidisciplinary approaches including systemic chemotherapy are essential [50].

Recently published ESTRO-ASTRO consensus paper strongly supports minimally invasive techniques for surgery are recommended to lessen treatment-related morbidity in oligometastatic NSCLC [38]. In addition, surgical resection of bone lesions is not a frequently selected approach because no superiority in terms of efficacy and safety is seen compared with radiotherapy. However, certain situations, such as patients showing acute neurologic signs due to spinal cord compression from bone metastatic lesions, may require immediate surgery for alleviation of symptom and prevention of related sequalae.

6. Timing of localized treatment to bone metastatic lesions

Careful pre-treatment planning of timing and sequence of LAT is vital when managing patients with bone oligometastases. The decision to implement preemptive radiotherapy or local consolidative systemic chemotherapy response should be made in consultation with a multidisciplinary team, including radiation oncologists, medical oncologists, and other specialists [13]. The team should consider the patient's overall clinical status, treatment goals, potential side effects of each approach, and the available evidence supporting these treatment options. Individual patient preferences and values should also be taken into account. The patients may benefit either from preemptive LAT and consolidative local treatment after an initial response to systemic treatment based on multiple factors (see Table 1).

6.1. Favoring preemptive LAT

Preemptive LAT to bone metastatic lesions has the advantage of reducing overall disease burden early, fostering responsivity to systemic treatment [51] and preventing early metastatic seeding. To maximize the treatment response of systemic anti-cancer treatment, for example immunotherapy, it is suggested that patients are more likely to benefit when disease burden is smallest [51]. Furthermore, in the immunotherapy setting, a potential abscopal effect from the combination of radiotherapy and immunotherapy can occur early when upfront radiotherapy is performed. It has been reported that concurrent radiotherapy

Table 1
Comparison of potential advantages and disadvantages between pre-emptive and consolidative local treatment of bone oligometastases.

	Pre-emptive	Consolidative
Advantages	*Early reduction of overall disease burden. *Increase responsivity to systemic treatment*Potential abscopal effect in immunotherapy setting (require more evidences) . *Early alleviation of symptoms in painful bone lesions	*Initial systemic chemotherapy may provide comprehensive control of both primary lung tumor and metastatic lesions. *Possibility of decreasing radiation fields and reducing radiation-related toxicity after the initial systemic chemotherapy response. *Time to observe initial clinical course of the disease.
Disadvantages	*Radiation field may be large and radiation-related toxicity may follow. *Risk of unnecessary toxicities in patients with poor performance and multiple comorbidities	* Bone -related symptoms can last longer *Cancer cells may earn time for treatment resistance due to development of spatial and temporary heterogeneity.

and immunotherapy or prior radiotherapy followed by immunotherapy result in reduction of non-irradiated tumor sites (Pembro-RT) [52]. Considering that metastatic bone lesions are often "difficult-to approach" for immune cells with anti-tumor activity, clinicians should pay attention to the synergistic effects. Studies have suggested that radiotherapy with a total dose of 30 Gy delivered in 10 fractions may help to induce an abscopal effect in bone metastases [53,54]. The use of immune checkpoint inhibitors before or after RT may help to optimize the effect of abscopal effect. On the other hand, according to a study by Gabani et al, the combination of SBRT and immunotherapy showed no improvement in outcomes in an unselected patient population when compared to immunotherapy alone [55]. Considering the somewhat contradictory studies, we can assume that the addition of SBRT to immunotherapy should not be solely performed for expectation of abscopal effect. In addition, more evidences are necessary to confirm specific patient population who can be benefited from abscopal effect.

Furthermore, preemptive radiotherapy to bone oligometastatic sites may help alleviate symptoms related to the bone metastasis, including pain, and potentially reduce the chance of complications related to bone metastases. This decision should account locations of metastatic lesions (spine vs non-spine, weight-bearing vs non-weight bearing), and whether patients complain associated symptoms.

It should be taken into consideration that only the patients with relatively good performance and conditions should be potential candidates of preemptive local treatment, otherwise patients may be at potentially avoidable and unnecessary risks associated with the preemptive ablative treatment. In addition, aggressive staging and imaging work-ups including PET-CT, bone scan and MRIs should precede the treatment in order to make sure that patients are appropriate treatment candidates and avoid progression of initially undiscovered metastatic sites.

6.2. *Favoring consolidative treatment*

On the other hand, when radiation is provided as a consolidative treatment, underlying treatment mechanisms include eradication of resistant clones after initial systemic treatment. Systemic chemotherapy target and control tumor cell throughout the body, including both primary lung tumor and metastatic lesions. Having an interval of systemic treatment before LAT may bring some clinical advantages, providing a chance of comprehensive approach to disease control.

A large radiation field may lead to increased risk of radiation-related toxicity [42,56], so decreasing the tumor size before therapy may decrease radiation fields of the metastatic burdens, decreasing the chance of treatment-related toxicity. Moreover, it allows time to observe the initial systemic response and reduce the disease burden of multiple lesions simultaneously. Recently published ESTRO-ASTRO guideline suggests that when implementing sequential local treatment after the initiation of systemic chemotherapy, at least 2–3 months of time period is necessary before restaging for assessing eligibility for localized treatment [38].

However, when approaching bone oligometastases specifically, there may be a risk of ongoing symptoms related to the bone metastases, as systemic chemotherapy alone may not alleviate the symptoms. Initial assessment of bone-related symptoms before the initiation of systemic treatment should come beforehand. Furthermore, during the period following exposure to initial systemic chemotherapy, acquired drug-resistant clones may emerge, and cells harboring the resistant mutations may proliferate to become part of dominant clones [57,58]. During the initial systemic treatment phase, tumor evolution can occur, leading to the diversification of cancer lineages and contributing to tumor heterogeneity [59]. This temporary tumor heterogeneity may exacerbate radioresistance [60], and reduce the effectiveness of subsequent localized radiotherapy.

7. Use of bone-modifying agents

Some studies have shown that bisphosphonates and denosumab reduced the incidence of SREs in lung cancer patients with bone metastases [61–63]. Bone-modifying agents have been frequently used to delay osteolytic bone metastatic lesions in several solid tumors. Recently, a series of studies on the efficacy of bisphosphonates and denosumab on bone metastatic lesions in advanced NSCLC has been reported. In a study including NSCLC and other solid cancers, zoledronic acid reduced the incidence of skeletal-related events [64]. In another study involving lung cancer patients with bone metastases, patients who received monthly denosumab showed a significant improvement in survival compared to the control group [65].

In a meta-analysis including 13 studies and 1,903 lung cancer patients, bone-modifying agents (bisphosphonates and denosumab) may have reduced SREs and bone pain [66]. In a study of 190 EGFR-mutation-positive NSCLC patients with bone metastases, use of denosumab showed a significant correlation with improved OS and prolongation of the survival period without SREs in a subgroup without preexisting SREs [67]. In a retrospective study of 110 advanced NSCLC patients with bone metastases, bone-targeted therapy improved the PFS (8.8 vs. 3.3 months, $P = 0.003$) compared to patients who did not receive additional bone therapy. All patients had five or fewer bone metastases, with the majority having fewer than three sites [68]. The addition of bone-modifying agents may be helpful in improving clinical outcomes and preventing skeletal-related events, but caution is needed regarding the increased risk of complications such as osteonecrosis of the jaw [69–71].

ESMO bone health guidelines also mention that bone-modifying agents can be used to reduce the risk of SREs as well as to treat hypercalcemia related to malignancy in patients with bone metastases, based on results of multiple randomized clinical trials. When selecting a bone-modifying agent, it is necessary to evaluate the specific drug, dose, and dosing interval based on individual patient factors. Clinicians should weigh the risk of SREs and the overall tumor control status when deciding whether to use a bone-modifying agent [72].

8. Ongoing studies

Up until now, there are not much evidences as to show detailed consensus strategy as to how we should approach bone oligometastases among metastatic NSCLC. Many prospective studies have been conducted regarding local consolidative treatment in oligometastatic cancer, but few focus on bone-only metastases. STEREO-OS, which evaluates the efficacy of SBRT added to systemic treatment in solid tumors including NSCLC, is a phase III study enrolling patients with three bone-only-metastatic lesions [73]. Patients are randomized to either of two arms (Arm A and Arm B). Patients enrolled in Arm A receive SBRT to all three oligometastatic bone lesions, while patients enrolled in Arm B receive only palliative radiotherapy if indicated [73]. This study is expected to provide clues to which patients are more likely to benefit from SBRT and further suggest optimal timing of the further localized treatment. Not confined to oligometastatic state only, there are changing trends in ongoing prospective studies include attempting various methods of radiotherapy when managing bone metastatic lesions. NCT05406063 compares multi-fraction SBRT and current standard of care of five-fraction SBRT for terms of improvement in pain [74]. The PERFACOOL (NCT03738670) study evaluates the efficacy of percutaneous radiofrequency ablation for pain relief in bone-metastatic lesions [75] (Table 2). Recently, an abstract was presented regarding the PERFACOOL study, which enrolled a total of 83 patients. Among them, 41 patients received a dose of 30 Gy, while 42 patients received a dose of 20 Gy. The study showed that the 20 Gy in 4 fractions twice a day regimen was noninferior to the standard 30 Gy in 10 fractions in terms of pain relief for complicated bone metastases. Furthermore, the alternative regimen demonstrated comparable safety in terms of acute toxicity

Table 2
Ongoing studies regarding treatment to bone metastatic diseases in patients with solid cancers.

Study	Design	Patients	Interventional arm	Control arm	Primary endpoint
STEREO-OS [73]	Phase III	Solid tumors including NSCLC	The efficacy of SBRT added to systemic treatment (Arm A)	Standard treatment plus palliative treatment allowed for symptoms (Arm B)	1-year PFS
NCT05406063 [74]	Open label, random-ized	All solid tumors	Multi-fraction SBRT within three treatment fractions	Current standard of care of five-fraction SBRT	Pain relief (response rate) measured with the VAS
NCT05101824 [87]	Single arm, multi-center, phase 2 study	Non-hematological cancer	All patients are treated with SABR. Two fractionation regimens (37.5 Gy in three fractions and 30.0 Gy in three fractions)	None	Local control rate at one-year post SABR
NCT03738670 Bipolar RFA of painful extra-spinal bone metastases (PERFACOOL) [75,76]	Single-arm, prospective, observational study	Multi-metastatic cancer patients with at least one painful lytic bone lesion	Procedure: Percutaneous RFA, single-session, percutaneous, extra-spinal bone metastasis destruction to achieve pain relief	None	Patient-reported pain improvement based on responses to the Brief Pain Inventory questionnaire
Short Course Accelerated RadiatiON Therapy (SHARON) NCT03503682 [88]	Randomized, multi-center study	Any solid tumor	Patients in this group are treated with 2000 cGy in four fractions administered twice a day (at least 6–8 h interval)	Patients in this group are treated with 3000 cGy in 10 daily fractions	Reduction of pain after radiotherapy, as assessed with VAS

Abbreviations: NSCLC, non-small cell lung cancer; Gy, gray; RFA, radiofrequency ablation; PFS, progression-free survival; SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative body radiotherapy; VAS, visual analogue scales.

and exhibited a lower rate of interruptions during radiation treatment [76].

Results of ongoing trials may further show specific clinical situations in which patients with bone oligometastases might benefit from local ablative treatment. This could help change ongoing trends of approaching bone oligometastases from the currently predominant palliative aim to a curative aim.

9. Proton therapies

Proton therapy is a novel form of radiation therapy that utilizes protons instead of X-rays. Its inherent advantages stem from the physical properties of particle therapy, which can reduce the side effects associated with traditional radiation therapy. This is achieved through the rapid dissipation of radiation at the “Bragg peak” with protons, minimizing exposure to normal tissues adjacent to the cancer site [77]. Consequently, side effects can be significantly reduced. The Bragg Peak is a distinct characteristic of proton radiation, whereby it delivers a high dose of radiation energy to cancerous tissues after traversing through the contiguous normal tissues in the body. This focused energy release can effectively eradicate cancer cells, and immediately disappear thereafter [78].

Thus, proton therapy allows for more precise and concentrated radiation therapy for local ablation, even in complex areas such as the pelvis and brain. It comes as no surprise that proton therapy is widely utilized for primary bone cancer nowadays [79].

In this regard, oligometastatic bone lesions show promise as potential candidates for proton therapy. In October 2022, Anthony et al. reported the results of the ’FAST-01 nonrandomized trial.’ They treated 12 metastatic sites in 10 patients using FLASH-enabled (≥40 Gy/sec) proton radiotherapy systems with a single-transmission proton beam. The treatment-related adverse effects were mild and consistent with conventional X-ray radiation therapy, while patient-reported pain scores showed a significant decline [80]. FLASH radiotherapy delivers radiation energy at an ultra-high dose rate that is much higher than current clinical practice [81]. In multiple preclinical studies, FLASH radiotherapy has shown to spare normal tissue while maintaining equivalent antitumor activity in comparison with conventional dose rate radiation treatment, which is known as the ’FLASH effect’ [82–85]. Additionally, a case report of a breast cancer patient with solitary sternal metastasis treated with proton therapy was recently published [86]. The authors concluded that proton therapy was a safe and effective treatment option, even when some of the targeted tissues were included in the re-irradiated area.

In general, proton radiation therapy is less commonly employed compared to X-ray radiation therapy due to its limited availability and higher cost. As a result, there is a scarcity of clinical data regarding the use of proton therapy for bone metastasis up until now. It is crucial to conduct more comprehensive clinical trials in the future to explore the potential of proton therapy and establish its efficacy in treating bone metastasis.

10. General recommendations in treating bone oligometastases

Recent consensus paper from ESTRO-ASTRO and the ESMO guideline on bone health provide general principles which could be helpful for managing bone oligometastases in NSCLC [38,72]. Based on the guidelines and results of recent studies, some recommendations for bone oligometastases can be made:

1) Stabilize bone metastatic lesions at high risk of fractures with surgical interventions, when appropriate.
2) Prioritize radiotherapy for painful bone lesions requiring immediate treatment.
3) If upfront radiotherapy to bone metastases does not provide evident clinical benefits, wait at least 3 months of systemic treatment, and reassess for potential benefit of localized treatment.
4) Reassess bone metastatic lesions after the initial response to systemic treatment. Consider associated symptoms, risk for SRE, disease burden, and expected reduction of bone metastases from further systemic treatment when deciding to implement localized treatment to bone oligometastases.
5) Use BMAs when they are expected to improve disease control, reduce the risk of SREs, and improve pain control in combination with systemic therapies.

11. Conclusion

In oligometastatic NSCLC, current trends of treatment are extending from palliative to curative objectives. However, it is unclear if pre-emptive curative treatment of bone oligometastatic lesions is superior to current palliative-based treatment. Ongoing trials will suggest efficacy and safety of curative-intent localized treatment in bone oligometastases of NSCLC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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