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Guidelines

ESTRO ACROP guidelines for external beam radiotherapy of patients with uncomplicated bone metastases

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ABSTRACT

After liver and lungs, bone is the third most common metastatic site (Nystrom et al., 1977). Almost all malignancies can metastasize to the skeleton but 80% of bone metastases originate from breast, prostate, lung, kidney and thyroid cancer (Mundy, 2002). Introduction of effective systemic treatment in many cancers has prolonged patients' survival, including those with bone metastases.

Bone metastases may significantly reduce quality of life due to related symptoms and possible complications, such as pain and neurologic compromise. The most serious complications of bone metastases are skeletal-related events (SRE), defined as pathologic fracture, spinal cord compression, pain, or other symptoms requiring an urgent intervention such as surgery or radiotherapy. In turn, growing access to modern diagnostic tools allows early detection of asymptomatic bone metastases that could be successfully managed with local treatment avoiding development of SRE.

The treatment for bone metastases should focus on relieving existing symptoms and preventing new ones. Radiotherapy is the standard of care for patients with symptomatic bone metastases, providing durable pain relief with minimal toxicity and reasonable cost-effectiveness. Historically, the dose was prescribed in one to five fractions and delivered using simple planning techniques. While 3D-conformal radiotherapy is still widely used for treating bone metastases, introduction of highlyconformal radiotherapy techniques such as stereotactic body radiotherapy (SBRT) have opened new therapeutic possibilities that should be considered in selected patients with bone metastases.

Introduction

After liver and lungs, bone is the third most common metastatic site [1]. Almost all malignancies can metastasize to the skeleton but 80% of bone metastases originate from breast, prostate, lung, kidney and thyroid cancer [2]. Introduction of effective systemic treatment in many cancers has prolonged patients' survival, including those with bone metastases.

Bone metastases may significantly reduce quality of life due to related symptoms and possible complications, such as pain and neurologic compromise. The most serious complications of bone metastases are skeletal-related events (SRE), defined as pathologic fracture, spinal cord compression, pain, or other symptoms requiring an urgent intervention such as surgery or radiotherapy. In turn, growing access to modern diagnostic tools allows early detection of asymptomatic bone metastases that could be successfully managed with local treatment avoiding development of SRE.

The treatment for bone metastases should focus on relieving existing symptoms and preventing new ones. Radiotherapy is the standard of care for patients with symptomatic bone metastases, providing durable pain relief with minimal toxicity and reasonable cost-effectiveness. Historically, the dose was prescribed in one to five fractions and delivered using simple planning techniques. While 3D-conformal radiotherapy is still widely used for treating bone metastases, introduction of highly-conformal radiotherapy techniques such as stereotactic body radiotherapy (SBRT) have opened new therapeutic possibilities that should be considered in selected patients with bone metastases.

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This guideline aims to comprehensively cover the diagnosis and local management of bone metastases with an emphasis on external beam radiotherapy. It compiles the available evidence for radiation oncologists and other medical professionals who treat patients with bone metastases, and gives recommendations for the following areas of relevance: diagnostic workup, including imaging and assessment of pain; indication and fractionation schemes for radiotherapy in different scenarios including pain reduction, remineralization and oligometastatic disease; and technical aspects of radiotherapy including target volume delineation and treatment planning. The levels of evidence and grades of recommendation follow the OCEBM "levels of evidence" [3].

From a clinical viewpoint, bone metastases can be divided into uncomplicated (approximately two thirds of cases) or complicated lesions [4]. The definition of complicated bone metastases varies across studies, but usually includes features suggestive of (impending) fracture, associated soft tissue mass or neurological deficits. The guideline has been divided in two parts, and the recommendations on management of complicated bone metastases are published separately [5].

Clinical scenarios of uncomplicated bone metastases

What is the definition of uncomplicated bone metastases?

The effect of radiotherapy on uncomplicated painful bone metastases has been extensively studied in numerous randomized controlled trials and meta-analyses [6–9]. Some of these studies formed the basis for the analysis of inclusion criteria for uncomplicated bone metastases [10]. The authors identified the following clinical characteristics which were pertinent in all investigated trials: pain from bone metastases, no impending or existing pathologic fracture or no spinal cord or cauda equina compression. They acknowledged that their definition of uncomplicated bone metastases may be incomplete. The absence of neuropathic pain and the absence of a soft tissue mass could not be incorporated as a characteristic of uncomplicated bone metastases, since soft tissue masses were not excluded in any of the studies examined and only two of the 21 studies included in the review excluded patients presenting with neuropathic pain. In addition, compression of spinal nerve roots is not mentioned specifically. Although these consensus descriptions are only derived from the overlap of inclusion criteria, they represent the best evidence for the definition of uncomplicated bone metastases.

Recommendation:

- Bone metastases – irrespective of size – should be regarded as uncomplicated if they are 1) painful; 2) without impending or existing pathologic fracture; and 3) without spinal cord or cauda equina compression, irrespective of size. [Grade B, Level 1]

What is the classification of oligometastatic bone disease?

The term oligometastases describes a stage IV patient with limited metastatic spread – a transitional state between localized and widespread disseminated disease, where radical local treatment might lead to long-term survival [11]. Although most published and ongoing studies used cut-offs varying from three to five metastases for inclusion [12], the actual median number of treated oligometastases is only one [13,14]. In a recent consensus, a group from the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) proposed a classification to account for the heterogeneity among patients with oligometastatic disease (OMD) [15]. De-novo OMD (i.e. first presentation of OMD) is distinguished from repeat (i.e. consecutive presentations with OMD) and induced OMD (i.e. OMD after previous polymetastatic disease). These groups are further subdivided into oligorecurrence, oligoprogression and oligopersistence, depending on whether the patient is under systemic therapy and whether the lesions are progressing. The classification might have prognostic value [16] and is currently being validated in clinical trials, such as the prospective observational OligoCare trial (NCT03818503) [17]. For patients with bone metastases, the oligometastatic state is relevant and besides symptom palliation improved (progression free) survival might become a relevant treatment goal.

Recommendation:

- Oligometastatic disease refers to a limited number of metastases and should be classified using the ESTRO-EORTC consensus classification. [Grade D, Level 5]

Box 1 Key recommendations: Classification of bone metastases

- Bone metastases – irrespective of size – should be regarded as uncomplicated if they are 1) painful; 2) without impending or existing pathologic fracture; and 3) without spinal cord or cauda equina compression, irrespective of size.
- Oligometastatic disease refers to a limited number of metastases and should be classified using the ESTRO-EORTC consensus classification.

Diagnosis and Investigation

What should be the diagnostic approach of screening patients for bone metastases?

Bone metastases can be found incidentally, in diagnostic procedures. Asymptomatic bone metastases are detected mostly in non-weight bearing bones.

A review of available European guidelines in bone metastases screening during initial staging and post-treatment follow-up in different primary cancers concluded that recommendations vary [18]. Thus, we recommend following disease-specific guidelines if clinical symptoms do not suggest bone metastases.

There is no single, optimal method for screening and evaluation of asymptomatic bone metastases. Commonly used modality is technetium labelled bone scan due to its availability and relatively low cost. Other methods enabling whole body imaging including (whole body) computed tomography (CT), magnetic resonance imaging (MRI) or 18F-FDG Positron Emission Tomography (^{18}F-FDG PET-CT) are also recommended, depending on their availability [18–21].

Recommendations:

- Following disease-specific guidelines for staging and post-treatment follow-up is recommended unless symptoms suggest bone metastases.

What should be the diagnostic approach for symptomatic bone metastases?

In patients with symptomatic bone metastases, CT or MRI are suggested for diagnosis and assessing risk of fracture, or spinal cord compression [18]. On the other hand, bone scintigraphy is a modality of choice for other symptomatic patients with prostate

and advanced breast cancer according to EAU and ESMO guidelines [22–24]. If bone scintigraphy is inconclusive and symptoms suggest bone metastases, hybrid imaging is recommended (e.g. ^{18}F-FDG-PET-CT). In advanced breast cancer, ^{18}F-FDG-PET-CT can be used instead of CT or bone scintigraphy if available [25]. Similar recommendations can be found for patients with symptomatic metastatic lung cancer: bone scintigraphy or ^{18}F-FDG-PET-CT are recommended as the first step of imaging [26]. Moreover, the localization of bone metastases plays a role in choosing the best modality for imaging as MRI is preferred to detect small bone lesions and outperforms other modalities in visualization of spinal metastases. MRI allows for the evaluation of the relation between bone lesion and spinal cord to assess spinal cord compression, soft tissues and bone marrow, all in multiplanar mode [27]. The rank order of modalities for accuracy in imaging bone metastases is MRI, CT, ^{18}F-FDG-PET-CT, bone scintigraphy and plain radiography for spine lesions, and ^{18}F-FDG-PET-CT, MRI, CT, plain radiography and bone scintigraphy for non-spine lesions [28].

Recommendations:

- Bone scintigraphy should be used to diagnose symptomatic bone metastases augmented by CT, PET-CT or MRI. [Grade C, Level 4]
- In acute onset of pain, CT or MRI is recommended. [Grade C, Level 4]
- In case of suspicious lesions detected in the spine, MRI is mandatory to assess potential infiltration of thecal sac, spinal cord, spinal nerves roots, bone marrow or soft tissues in case of suspected extension beyond the bony compartment. [Grade C, Level 4]

What are indications to obtain a bone biopsy for pathological examination?

Bone biopsy should be considered in case of known primary cancer with a long disease-free interval from the primary diagnosis and occurrence of bone metastases if there is no other evidence of metastatic recurrence [29]. It might be considered in case of oligometastatic disease or cancers with known molecular aberrations that are susceptible for hormonal or targeted therapies, for example breast and lung cancer or malignant melanoma. If bone biopsy is indicated, CT-guided fine needle biopsy is a satisfactory method to confirm metastatic spread to bones [30,31]. In case of cancers of unknown primary or requiring higher diagnostic accuracy or molecular profiling, core biopsy delivers more valuable data [32,33].

Recommendations:

- Consider fine needle CT-guided biopsy for suspected bone lesions that require diagnostic confirmation. [Grade C, Level 4]
- Core biopsy should be considered in case of bone metastases without known primary tumour site and in cancers where molecular profiling may open new therapeutic possibilities. [Grade C, Level 4]

What is the role of biochemical markers in diagnosis of bone metastases?

Despite numerous attempts of pre-clinical and clinical assessment of biochemical markers as diagnostic and prognostic markers in patients with bone metastases, none of them can be currently recommended in routine clinical practice and validation in controlled prospective trials is warranted [34].

Recommendation:

- The routine use of any biomarker of bone metabolism to diagnose or monitor bone metastases is not recommended. [Grade C, Level 3]

Box 2 Key Recommendations: Diagnosis and Investigation in symptomatic bone metastases

- Following disease-specific guidelines for staging and post-treatment follow-up is recommended unless symptoms suggest bone metastases.
- Bone scintigraphy should be used to diagnose symptomatic bone metastases augmented by CT, PET-CT or MRI.
- In case of suspicious lesions detected in the spine, MRI is mandatory to assess potential infiltration of thecal sac, spinal cord, spinal nerves roots, bone marrow or soft tissues in case of suspected extension beyond the bony compartment.
- Core biopsy should be considered in case of bone metastases without known primary tumour site and in cancers where molecular profiling may open new therapeutic possibilities.

Clinical assessment and response evaluation

What is the recommended clinical assessment of a patient presenting with uncomplicated bone metastases?

A clinical assessment should include the following items:

- a comprehensive history of pain including pain score and pain provoking positions;
- use of pain medication and its compliance;
- medical and surgical history;
- an assessment of the performance status;
- an estimation of the expected survival;
- physical examination with awareness of referred pain, consider marking of painful sites on planning CT scan;
- interpretation of radiologic scans in combination with the patient's history and physical examination.

Depending on their size and location, bone metastases can cause somatic and neuropathic pain. The minimum assessment of pain in the clinical setting uses a rating scale such as the numeric rating scale or visual analogue scale.

When surgery is one of the treatment options, estimation of survival is important in selecting the appropriate treatment for patients with bone metastases. In patients with spinal bone metastases, primary tumour, performance status and the American Society of Anesthesiologists physical status classification are the factors that are most often associated with survival [35–37]. However, estimating survival in cancer patients is difficult for physicians and individual predictions may deviate significantly from actual survival [38]. Models to predict survival in patients with spinal bone metastases have been developed by several authors as detailed in the section on metastatic spinal cord compression in the second part of this guideline [39–43].

Recommendation:

- The minimal clinical assessment of a patient with uncomplicated bone metastases includes a pain score, performance status and an estimation of the predicted survival. [Grade C, Level 3]

What is the recommended clinical and imaging assessment for response evaluation during follow-up?

Clinical evaluation of pain and function remains the most important assessment of response to treatment. However, imaging assessment of bone metastases after treatment might be necessary in clinical trials, for differential diagnosis, or for patients treated with treatment intents such as local control or remineralisation. For these patients, follow-up imaging may be considered (every) three to six months after radiotherapy [44,45]. The RECIST criteria are not fully applicable for bone metastases evaluation, thus the MD Anderson (MDA) criteria for response of BM have been developed in which sclerosis in treated bone metastases based on CT, MRI, or bone scintigraphy imaging is used as a marker of response and sign of bone healing. Complete response can be diagnosed when lytic lesions are completely filled-in or sclerotic in CT and plain radiography, all hot spots have disappeared in bone scintigraphy, CT or MRI, or osteoblastic lesions are normalized in CT and plain radiography. Partial response is defined as appearance of a sclerotic rim and partial fill-in or sclerosis of lytic lesions, sclerosis of previously undetected lesions on plain radiography or CT, and regression of lesions on MRI, CT and bone scintigraphy. If increase of size or activity of bone metastasis is observed on CT, MRI and bone scintigraphy or a new lesion appears, progressive disease is diagnosed. In comparison with previous classifications, e.g. WHO and UICC, the MDA criteria correlate better with clinical response in patients with metastatic breast cancer and better predict progression-free survival in responders [46].

The optimal timing and imaging modality for response evaluation is not clearly defined. Bone scintigraphy is not a reliable tool in the first three to six months after treatment due to the possibility of flare phenomena in healing bones and in osteolytic metastases with low bone turnover, results of bone scintigraphy might be false negative due to decreased uptake of isotope in bones with low osteoblastic activity but rapidly progressive disease [21,47].

CT and whole body MRI allow for earlier evaluation of lesions after treatment. The role of molecular imaging including PET/CT is still to be determined in monitoring of post-treatment changes in bone metastases. Data published so far, although promising, need further validation to reach evidence based level [48,49].

Recommendations:

- Clinical evaluation of pain and function is sufficient for assessment of response to treatment, and routine imaging is discouraged after treatment of uncomplicated bone metastases for response assessment. [Grade C, Level 3]
- Response assessment via imaging could be considered for patients in clinical trials or for patients treated with the intent of local control or remineralisation. [Grade C, Level 4]

Box 3 Key recommendations: Assessment and pain measurement

- The minimal clinical assessment of a patient with uncomplicated bone metastases includes a pain score, performance status and an estimation of the predicted survival.
- Routine imaging is discouraged after treatment of uncomplicated bone metastases for response assessment.

Indications and treatment aims of radiotherapy for uncomplicated painful bone metastases

What is the role of radiotherapy in the treatment of painful uncomplicated bone metastases?

Conventional radiotherapy can achieve a clinical significant pain response in up to 80% of treated patients with a median response duration of 18–21 months. It is widely accepted as the standard of care for palliative treatment of uncomplicated metastatic bone pain, despite the absence of randomized trials comparing radiotherapy with sham radiotherapy or with other pain killing strategies such as opioids or surgical options [50,51]. Only one randomized trial compared samarium-153 with or without conventional radiotherapy in patients with painful metastatic prostate cancer with multiple bone lesions, demonstrating a significant improvement in pain relief if radiotherapy was added [52].

In case of diffuse pain from disseminated bone metastases, hemibody or wide field irradiation – a simple anterior-posterior large-field technique to cover the supra- or infra-diaphragmatic area – can provide a substantial and rapid pain response as found in several clinical trials and prospective studies [53–58]. Moreover, it is considered cost-effective [59]. The used fractionation regimens vary in the literature; however, the most frequent is 6 Gy in one fraction for the upper part of the body and 8 Gy in one fraction for the lower part. For the latter anti-emetic IV prophylaxis is indicated for at least 12 hours.

Patients with widespread disseminated painful osteoblastic or mixed pattern bone metastases of prostate cancer should be considered receiving radionuclide therapy (e.g. radium-223, strontium-89 or samarium-153).

Recommendations:

- Conventional radiotherapy should be used to treat uncomplicated painful bone metastases, especially if pain is not sufficiently controlled by pain medication or when a reduction of pain medication is desired. [Grade A, Level 1]
- For diffuse pain caused by multiple bone metastases single fraction hemibody or wide field irradiation should be considered. [Grade A, Level 1b]
- Radionuclide therapy can be considered as a palliative treatment in patients with painful osteoblastic or mixed pattern bone metastases of prostate cancer. [Grade A, Level 1a]

What is the recommended fractionation scheme for treatment of pain from uncomplicated bone metastases?

An updated review of randomized trials continues to show equivalent outcomes in pain control and toxicity after a single dose of 8 Gy compared to multiple fraction radiotherapy in patients with uncomplicated bone metastases [9]. Overall response rate is 61% after single fraction and 62% after multiple fraction radiotherapy. In assessable patients only, this number increases to 72% and 75%, respectively. Although patients with more favourable survival show better response rates, even in this patient group, no difference between single and multiple fraction radiotherapy was demonstrated [60]. Retreatment rates are increased in patients treated with single fraction radiotherapy (20%) compared to multi-fraction radiotherapy (8%) [9]. As time to pain progression is similar after single and multiple fractions, this may reflect increased willingness to retreat patients after initial single fraction compared to multi-fraction radiotherapy [50]. While quality of life

and cost effectiveness benefits may be assumed from shorter fractionation schedules, both have not been studied as primary endpoints in the respective trials. Therefore, a clear recommendation cannot be given in this context, but potential benefits of shorter treatment times should be considered.

It has been hypothesized that SBRT might improve pain response compared to conventional radiotherapy techniques. Currently, six randomised trials comparing conventional radiotherapy with SBRT for patients with spinal and non-spinal bone metastases have been published with conflicting outcomes [61–66]. SBRT fractionation regimen varied from 12–24 Gy in a single fraction, 24 Gy in two fractions, 30 Gy in three fractions, or 35 Gy in five fractions. Aligning the results of these trials, and looking at the overall response rates for pain in the intention-to-treat population at three months, four trials including over 600 patients did not find a significant difference between conventional radiotherapy and SBRT [62–63,66]. The trial of Berwouts et al. reporting pain response at one month, also showed that SBRT did not improve pain response [61]. Only the study of Sahgal et al., comparing conventional radiotherapy at a dose of 20 Gy in five fractions to SBRT at a dose of 24 Gy in two fractions, found that SBRT statistically significantly improved the complete response rate three months after treatment [65]. These trials do not support the routine use of SBRT in patients with bone metastases with regard to pain response. Future efforts should focus on identifying subgroups of patients who are likely to benefit from SBRT.

Recommendation:

- Patients with uncomplicated painful bone metastases should be treated with a single fraction of 8 Gy. [Grade A, Level 1]
- Current randomized trials do not support the routine use of SBRT in patients with painful bone metastases. [Grade A, level 1]

What are the common side effects of radiotherapy for bone metastases?

Side effects of radiotherapy are dictated by which tissues receive a substantial dose. Irradiation of metastases in the axial skeleton and pelvic bones is most prone to side effects because of nearby organs. For example, conventional radiotherapy to lumbar spine metastases will usually involve irradiation of the bowels, possibly resulting in nausea and abdominal discomfort. Side effects after conventional radiotherapy are however very modest, with the majority of patients experiencing no acute toxicity [6,9]. Radiation induced nausea and vomiting is best controlled by 5-hydroxytryptamine-3 receptor antagonists (e.g. ondansetron) [67,68], and optionally daily dexamethasone [69–71].

Generally, treatment is associated with fatigue in at least two thirds of patients [72]. In addition, up to 44% of patients experience a pain flare in the first week after treatment, which resolves within a median of one to three days [73]. After SBRT, the reported pain flare is higher (10 to 68%). Pain flare can be managed by symptomatic measures such as paracetamol and dexamethasone. In the management of pain flare, only studies comparing prophylactic use of glucocorticoid vs. placebo have been performed [74]. The SC.23 randomized trial showed that prophylactic use of dexamethasone in patients with bone metastases undergoing a single dose of 8 Gy significantly reduced the pain flare incidence from 35% (with placebo) to 26% (with 8 mg dexamethasone for five days) [75]. The DEXA randomized trial however did not find that prophylactic intake of dexamethasone had an effect on the pain flare incidence after radiation, although an immediate effect on pain was observed [76]. There is no consensus regarding the routine use of dexamethasone for all patients undergoing radiotherapy for bone metastases [77].

A serious late effect is the occurrence of radiation induced vertebral compression fractures. Reports of spinal SBRT show that the risk of a compression fracture ranges from 11% to 39% which is higher than those seen with conventional radiation (<5%) [9,78]. The risk of fracture significantly increases as the dose per fraction increases beyond 19 Gy [79].

Recommendations:

- As the majority of patients experience no or mild acute toxicity after conventional radiotherapy, the possibility of experiencing side effects should not be a reason to withhold patients with bone metastases from this treatment. [Grade A, level 1a]
- Pain flare, occurring in around one third of patients, could be managed by symptomatic measures such as paracetamol or dexamethasone. [Grade D, level 5]

Which patients should be considered for re-irradiation?

Most patients with bone metastases are treated with the intent to relieve pain. The median time to response is three to four weeks [51,80]. Therefore, assessment of the treatment effect should include the pain score including analgesic use at least four weeks after radiotherapy. Patients with no pain relief or pain progression after initial radiotherapy, or patients with a pain relapse after initial response should be considered for re-irradiation. Response should preferably be measured by the criteria in the International Consensus Working Party recommendations [81]. According to these recommendations, patients with a pain reduction of at least two points on a 11-point scale without an increase in analgesic use, or a 25% or more reduction in opioid use without an increase in pain score, are having a meaningful response to treatment. A meta-analysis including seven studies evaluated the effectiveness of re-irradiation for painful bone metastases and found a pooled overall response rate of 58% (95% CI 0.49–0.67) [82]. One randomized trial compared a single dose of 8 Gy with a fractionated schedule in re-irradiation of patients at least four weeks from initial radiotherapy with persistent or recurrent pain [83]. In those available for assessment at two months after treatment the pain response was 45–51% which was independent of pain response to previous radiotherapy or previous radiation fractionation scheme.

Recommendations:

- The minimal assessment of the treatment effect is the pain score including any changes in analgesic use at least 4 weeks after radiotherapy. [Grade B, Level 3]
- Patients with insufficient pain relief, no pain relief or pain relapse after initial radiotherapy, should be considered for re-irradiation. [Grade A, Level 1]

What is the recommended fractionation scheme for the retreatment of pain from uncomplicated bone metastases?

One randomized, non-inferiority trial including 850 patients needing re-irradiation compared the pain relieving effect of 8 Gy in a single dose to 20 Gy in multiple fractions of 2.5 or 4 Gy [83]. In the intention-to-treat population, response two months after single fraction radiotherapy was non-inferior to multi-fraction radiotherapy (28% vs 32%). In addition, 8 Gy in a single dose was associated with fewer adverse events than the fractionated schedule.

Recommendation:

- For re-irradiation of patients with uncomplicated painful bone metastases, a single fraction of 8 Gy is recommended. [Grade A, Level 1]

Is there a role for preventive radiotherapy in patients with multiple bone metastases in the absence of pain?

The introduction of modern systemic therapies has improved the life expectancy of patients with metastatic disease resulting in more patients living long enough for skeletal complications to develop [35]. In addition, side effects of radiotherapy are less likely to occur with increasingly more conformal techniques. Theoretical benefits of early, upfront radiotherapy to asymptomatic bone metastases include reducing the risk for SREs, developing painful bone metastases, and improving pain-free survival. One retrospective study assessed the use of conventional radiotherapy (dose and technique not documented) in patients with asymptomatic bone metastases [84]. Only 16% of the 171 included patients received radiotherapy, but the median time from diagnosis of asymptomatic bone metastases to pain or an SRE was 81 months, in comparison to 25 months in the untreated group. Currently, one randomized trial is recruiting patients with asymptomatic 'high risk' (such as bulky disease or disease involving the hip or junctional spine) bone metastases to prophylactic radiotherapy vs. observation [85]. It is, however, unclear yet how to select patients with asymptomatic bone metastases that will become painful. For patients with lesions that are at risk for fractures (e.g. femoral lesions with more than 30 mm axial cortical involvement), prophylactic radiotherapy might prevent fractures [86], as is discussed in more detail in the guideline on complicated bone metastases [5].

Recommendation:

- The administration of preventive conventional radiotherapy is not generally recommended for asymptomatic uncomplicated bone metastases due to current lack of clear evidence. [Grade C, Level 4]

Is there a role for treating oligometastatic bone disease with SBRT irrespective of pain?

There are no randomized trials assessing the effectiveness of an ablative treatment in patients with oligometastatic bone disease only. The SABR-COMET randomized phase 2 trial assessed the effect of treating all oligometastatic disease (maximum of five lesions) with SBRT (allowable doses ranged from 16–60 Gy in one to eight fractions), with standard of care, including radiotherapy to the standard principles of palliative radiation (i.e. alleviating symptoms or preventing anticipated complications of progression) [87,88]. Bone metastases accounted for around one third of the treated lesions. SBRT was associated with a 22-month improvement in median overall survival and a doubling of median progression free survival, however with an increase in toxicity and a 5% treatment-related mortality in the SBRT group. As patients have not been stratified by dose and fractionation scheme, no firm conclusions can be drawn from this trial regarding the preferred treatment regimen for patients with oligometastatic (bone) lesions. Of note, all patients in the SABR-COMET trial had a controlled primary tumour and a median time of at least 2 years from diagnosis. Prostate cancer was over-represented in the SBRT arm and bone metastases to the femoral bone were an exclusion criterion. The generalizability of the results might therefore be limited, and the impact of SBRT might differ between de-novo, repeat and induced oligometastatic disease [15].

Recommendation:

- Patients with oligometastatic bone lesions may be offered local ablative SBRT but should be carefully informed about the potential risks and benefits, while evidence for an overall survival benefit from phase 3 trials is still lacking. [Grade B, Level 2b]

What is the evidence for using high-dose radiotherapy to treat pain from oligometastatic bone disease?

The subgroup of patients with oligometastatic bone disease may represent a favourable subgroup that might benefit from a higher radiotherapy dose. In the Dutch Bone Metastasis Study, however, no difference in pain response was seen in patients surviving more than one year after a single fraction of 8 Gy or fractionated conventional radiotherapy [60]. An analysis of the prospective PRESENT cohort including those patients with oligometastatic bone disease showed higher clinical local control rates after SBRT compared to conventional radiotherapy, but SBRT did not improve pain response, duration of response or quality of life [89]. No difference in pain response was seen after stratification by radiation dose (8 Gy in one fraction vs 30 Gy in 10 fraction vs SBRT).

Recommendation:

- There is no advantage to higher dose conventional radiotherapy or SBRT over single dose conventional radiotherapy for pain response in oligometastatic bone disease. [Grade B, Level 1b]

Box 4: Key Recommendations: Indications and aims of radiotherapy

- Conventional radiotherapy should be used to treat uncomplicated painful bone metastases, especially if pain is not sufficiently controlled by pain medication or when a reduction of pain medication is desired.
- For diffuse pain caused by multiple bone metastases single fraction hemibody or wide field irradiation should be considered.
- Patients with uncomplicated painful bone metastases should be treated with a single fraction of 8 Gy.
- As the majority of patients experience no or mild acute toxicity after conventional radiotherapy, the possibility of experiencing side effects should not be a reason to withhold patients with bone metastases from this treatment.
- Patients with insufficient pain relief, no pain relief or pain relapse after initial radiotherapy, should be considered for re-irradiation with a single fraction of 8 Gy.
- There is no advantage to higher dose conventional radiotherapy or SBRT over single dose conventional radiotherapy for pain response in oligometastatic bone disease.

Radiotherapy techniques

Is there a preferred treatment planning technique for painful bone metastases?

Different treatment techniques are applied for palliative radiotherapy of bone metastases, from simple single or parallel-opposed static field simulation and static fields for 3-dimensional radiation therapy (3DCRT) to more complex and conformal intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy

(VMAT). Conformal treatment techniques have the advantage of sparing normal tissue thereby theoretically reducing radiation-induced toxicities and allow for dose escalation. Conformal treatment techniques are, however, more expensive and resource intensive due to their complexity and need for increased quality control. Simple static field treatments reduce the need for contouring and complex dosimetric calculations making them time-effective. While conformal treatment techniques have been widely adopted into clinical practice, randomized evidence indicating superior outcomes with regards to efficacy or toxicity reduction is lacking. The ongoing SUPR-3D (NCT03694015) randomized phase III trial is comparing patient-reported quality of life related to radiation induced nausea and vomiting between simple unplanned palliative radiotherapy using static fields and VMAT in patients with bone metastases [90].

Recommendation:

- There is no evidence yet that any technique is superior when delivering palliative radiation doses. Both simple conventional and conformal techniques can be considered on an individual patient level. [Grade D, Level 4]

Which target volume concept should be used for treating uncomplicated painful bone metastases?

The advent of conformal radiotherapy and image-guidance has moved radiotherapy for bone metastases from simulation of treatment fields based on bony landmarks and inclusion of whole bone or vertebrae to treating defined target volumes according to ICRU 50. Bone metastases target volumes may vary depending on the type of bone (long, short, flat, sesamoid, irregular), the presence of extraosseous extension and, in post-operative cases, the presence of surgical implants and the location of the surgical access.

Still, for conventional radiotherapy, no consensus or recommendation exists for a specific target definition beyond the commonly used simulation portal-field based approach. For spinal metastases, the target volume includes one additional vertebra above and below the affected vertebrae and the field borders are set to the intervertebral space and the transverse processes. If a 3D-CT or MRI-based target definition is being used, it is highly recommended to use a GTV-, CTV- and PTV-based contouring approach and to depart from the simulation based field borders.

Expert consensus recommendations only exist for target volume delineation specific to (postoperative) spinal SBRT [91,92]. However, different concepts for target volume definition have not been compared in randomized trials. The ongoing DOSIS trial (NCT02800551) is a randomized phase II trial comparing pain response in patients treated with dose-intensified fractionated SBRT and conventional radiation therapy for painful spinal metastases [93,94]. In the experimental SBRT arm, the target consists of the entire affected vertebrae (conventional dose PTV) and an integrated boost to the macroscopic tumour (high-dose PTV), thus combining conventional and SBRT target volume concepts. Similarly, a simultaneously integrated boost to the GTV in spinal metastases has been proposed, with the CTV consisting of the surrounding bony compartment, in order to mitigate the risk of vertebral compression fracture [95]. The effect of this concept will be prospectively validated using data from the VERTICAL study [96,97].

Little consensus exists also for non-spinal metastases. For conformal radiotherapy, the gross tumour volume (GTV) may be defined using CT, MRI or PET-CT. A clinical target volume (CTV) may be created either by isotropic expansion of the GTV, or by delineation of the affected bone compartment. A retrospective series found that compartmental CTVs in pelvic bone metastases are associated with improved pain control and local control [98]. However, no high level evidence or consensus exists favouring one CTV-concept above the other.

Recommendations:

- In case of 3D conformal image guided radiotherapy, a target definition according to ICRU 50 including a CTV and PTV should be preferred for uncomplicated bone metastases. [Grade D, Level 4]
- CTV-based radiotherapy should be strongly considered when there is soft tissue mass or extension of the bone metastasis. [Grade D, Level 4]

Box 5: Key recommendations: Radiotherapy techniques

- There is no evidence yet that any technique is superior when delivering palliative radiation doses. Both simple conventional and conformal techniques can be considered on an individual patient level.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.05.024.

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