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Review Article

Advances in radiotherapy in bone metastases in the context of new target therapies and ablative alternatives: A critical review

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ABSTRACT

In patients with bone metastases (BM), radiotherapy (RT) is used to alleviate symptoms, reduce the risk of fracture, and improve quality of life (QoL). However, with the emergence of concepts like oligometastases, minimal invasive surgery, ablative therapies such as stereotactic ablative RT (SABR), radiosurgery (SRS), thermal ablation, and new systemic anticancer therapies, there have been a paradigm shift in the multidisciplinary approach to BM with the aim of preserving mobility and function survival.

Despite guidelines on using single-dose RT in uncomplicated BM, its use remains relatively low. In uncomplicated BM, single-fraction RT produces similar overall and complete response rates to RT with multiple fractions, although it is associated with a higher retreatment rate of 20% *versus* 8%.

Complicated BM can be characterised as the presence of impending or existing pathologic fracture, a major soft tissue component, existing spinal cord or cauda equina compression and neuropathic pain. The rate of complicated BM is around 35%. Unfortunately, there is a lack of prospective trials on RT in complicated BM and the best dose/fractionation regimen is not yet established.

There are contradictory outcomes in studies reporting BM pain control rates and time to pain reduction when comparing SABR with Conventional RT. While some studies showed that SABR produces a faster reduction in pain and higher pain control rates than conventional RT, other studies did not show differences. Moreover, the local control rate for BM treated with SABR is higher than 80% in most studies, and the rate of grade 3 or 4 toxicity is very low. The use of SABR may be preferred in three circumstances: reirradiation, oligometastatic disease, and radioresistant tumours. Local ablative therapies like SABR can delay change or use of systemic therapy, preserve patients' Qol, and improve disease-free survival, progression-free survival and overall survival. Moreover, despite the potential benefit of SABR in oligometastatic disease, there is a need to establish the optial indication, RT dose fractionation, prognostic factors and optimal timing in combination with systemic therapies for SABR.

This review evaluates the role of RT in BM considering these recent treatment advances. We consider the definition of complicated BM, use of single and multiple fractions RT for both complicated and uncomplicated BM, reirradiation, new treatment paradigms including local ablative treatments, oligometastatic disease, systemic therapy, physical activity and rehabilitation.

Bone metastases (BM) can affect quality of life (QoL) and may impact on patient survival. They require the care of a multidisciplinary team [1–3]. These patients are candidates for a variety of treatments, ranging from supportive care to surgery or ablative therapies, such as radiosurgery (SRS), stereotactic ablative RT (SABR) and image-guided thermal ablation [3,4]. In any treatment schedule involving BM patients, the overarching goal of palliative radiotherapy (RT) remains to deliver an effective, safe, and timely treatment in as few fractions as possible, recognizing the patient's life expectancy.

The clinical management of painful BM should include optimal analgesia, osteoclast inhibitors to reduce skeletal-related complications and systemic therapy. Conventional chemotherapy can

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reduce pain and improve QoL in a subset of patients with BM [5]. For prostate cancer patients with diffuse bone pain and multiple BM, half body RT has been largely replaced by bone-targeting radioactive isotopes [6]. Other systemic therapies may be used depending on the cancer type, including hormonal therapy, immunotherapy, and targeted therapy. These, in conjunction with the concept of radical treatment for oligometastases, have resulted in potential for improvement in the survival of selected metastatic cancer patients.

Methods

Between January 2021 and June 2021 a review was performed using Medline with the terms: bone metastases and radiotherapy. Specific research questions were approached by searching for combinations of the following keywords: stereotactic body radiotherapy, SBRT, stereotactic ablative RT, SABR, cyberknife, stereotactic radiosurgery, SRS, spinal metastases, non-spine bone metastases, spinal cord compression, prognostication, systemic treatment, chemotherapy, targeted therapy, hormonal therapy, immunotherapy, side effects, toxicity, spinal cord tolerance, re-irradiation, rehabilitation. Articles published in English until May 31th, 2021 were selected for relevance to the multidisciplinary management of bone metastases with surgery, radiotherapy or systemic anticancer treatment. All citations were evaluated for relevant content and validity.

Radiotherapy in uncomplicated BM

Over the last twenty years, a number of prospective randomised trials have been conducted with regards to the optimal RT dose fractionation schedule to palliate pain in uncomplicated BM, with similar pain relief response rates for single or multiple fractions RT in both intention-to-treat and per protocol assessable cohorts [7–9]. A systematic review and meta-analysis, with data from 29 randomized trials, found that the overall response rate was 61% for single-fraction RT (1867/3059 patients) *versus* 62% in RT with multiple fractions (1890/3040), and the complete response rate was also similar for both groups (23% *versus* 24%, respectively) providing level I evidence on the management of simple BM [9]. In contrast, the retreatment rate was 20% in the single dose group (497/2482) *versus* 8% in the multiple fraction group (192/2468) ($p < 0.01$) [9].

Despite the advantages of single fraction RT in patients with uncomplicated BM, in a Medicare cohort with 7547 patients with BM from breast cancer, only 4% of patients were treated with single fraction, and 40.9% received RT with 10 or more fractions [10]. In a recent review, designed to analyse real-world data, amongst those cases with painful BM, only 12.9% were treated with a single fraction of 8 Gy [11]. An evaluation of behavioural determinants in the choice of single-dose RT in uncomplicated BM found in semi structured interviews with 38 radiation oncologists from 10 different provinces in Canada, the two principal impediments to single fraction RT use were the higher risk of retreatment after single fraction RT (82%, $n = 31$) and worries about BM near the spine and with large target volumes (74%, $n = 28$) [12]. Nevertheless, implementing a radiation oncology service dedicated to palliative care increased the use of single-fraction RT from 6.4% to 22.3% ($p < 0.001$) [13]. One possible reason for the increase in short course RT could be better alignment between doctors' and patients' expectations concerning treatment goals [13]. Moreover, a comprehensive knowledge translation campaign in Manitoba increased single fraction RT use from 38% in 2016 to 59% in 2017 [14].

Radiotherapy in complicated BM

The American Society for Radiation Oncology (ASTRO) BM consensus recognizes the need to define complicated BM more appropriately to improve the BM therapy decision process [15]. The absence of a clear definition of complicated BM makes it difficult to determine which BM patients the prospective randomized trial results apply to. Despite some controversies, complicated BM might be described as BM with the following features: impending or existing pathologic fracture, a major soft tissue component, spinal cord or cauda equina compression, and neuropathic pain [16].

The limitation to classifying patients as uncomplicated BM or not often comes from the lack of detailed description of radiographic evidence or clinical factors like the presence of impending pathological fracture and compression of the spinal cord and peripheral nerves [17,18]. The most common exclusion factors in these trials were fracture or its impending risk in 78% (18/23), previous RT in 78% (18/23), and the presence of neuraxis compromise in 65% (15/23) of studies [18]. Unfortunately, these debilitating complications are frequent and will become even more common as patient longevity increases from improvement in systemic anticancer treatment. The incidence of BM with a soft tissue or extra osseous component, pathologic fracture, or spinal cord compression has been reported as high as 31%, 35%, and 15%, respectively [19,20]. One study showed that in 927 BM, 28.6% of the patients had fractures, 24.4% had soft tissue extension of the metastases, 8.7% compression in the spinal cord, and 2.9% cauda equina compression [14]. A reviewing of data from 401 patients observed a 20.6% incidence of pathological fracture, 38.6% of soft tissue mass, 8.9% of prior surgery, 4.4% with previous RT, and 52 % neurological compromise of spine and medial pelvis [18]. When considering the more usual description of complicated BM (pathological fractures and neuraxis compromise without the other characteristics), a rate of 36.4% was described [18]. This rate of complicated BM is similar to the rate of 34% observed in 4127 BM treated with RT in other centres [14,20].

Considering the worse median survival in complicated BM patients, it is imperative to minimize patient burden and prioritize convenience by utilizing short course RT schedules whenever possible [21]. In terms of resources, single-dose RT is more cost-effective than more protracted RT schedules, and treatments with palliative intent can represent close to 30% of daily practice in a RT department [22,23]. The use of more protracted RT courses in BM patients can substantially increase the RT department workload [24]. In any treatment schedule involving complicated BM patients, the overarching goal of palliative RT remains delivery of an effective, safe and timely treatment in as few fractions as possible, respecting the patient's expectations.

Impending or actual pathological fracture

In complicated BM patients, surgery provides bone stabilization, tumour debulking, and, as a result, reduces pain and improves QoL [25]. For BM in long bones, surgery is recommended for impending or pathological fracture [26]. BM with Myrels scores ≥ 8 usually require prophylactic fixation before RT, and tumours with scores ≤ 7 can receive RT only [26]. Post-operative RT is usually given to improve local control, reduce pain, improve bone repair and functional outcomes [27]. In BM with impending or pathologic fracture, several RT schedules are used in post-operative or sole treatment. There is little supporting evidence because these patients were excluded in most phase 3 trials. It is currently unknown whether one or two dose schedules are as effective as the more conventional schedules, such as 20 Gy in 5 fractions or 30 Gy in 10 fractions.

In a retrospective study, 60 BM patients with impending or actual pathologic fractures, postoperative RT increased the probability of achieving a functional status: 53% *versus* 11.5% in patients with surgery alone ($p < 0.01$) [28]. With surgery alone, 15% of the fixated sites (4/26) required a subsequent orthopaedic procedure after a mean time of 12.5% *versus* 3% in the postoperative RT group ($p = 0.03$). Evaluation of best functional status and the RT course did not reveal any clear dose–response relationship, although 19 out of 26 patients received 30 Gy in the surgery plus postoperative RT arm [28].

More pathologic fractures with single-fraction RT (3%) than with multiple fraction treatment (1.6%) have been reported but an associated test for heterogeneity was statistically not significant ($p = 0.34$) [7]. Overall, the risk of developing a pathologic fracture was almost double in the single fraction arm when compared to multiple fraction RT [7].

Spinal cord compression (SCC)

For many spinal BM patients, surgical intervention is the initial recommendation for SCC or spine instability [29]. Axial stability and indications for a surgical consultation are identified with the Spinal Instability Neoplastic Score (SINS) [29]. For SCC patients, combined therapy (surgery plus post-operative RT with conventional dose) improved outcomes with 84% (42/50) of the patients being able to walk after treatment *versus* 57% in the RT alone arm [30]. For patients who were incapable of walking, surgery resulted in a higher recovery rate in walking ability (62% *versus* 19%, $p = 0.01$) [30]. Patients who underwent surgery retained the ability to walk longer than in the RT alone (median 122 days *versus* 13 days, $p = 0.03$) [30]. Surgery techniques such as vertebroplasty or kyphoplasty do not obviate the need for adjuvant RT [15]. In 1997, Maranzano *et al* treated 53 poor prognosis patients defined by radioresistant tumours or radiosensitive histologies in patients with plegia, paresis, ECOG performance status ≥ 2, and/or short life expectancy who had SCC and determined the safety profile and efficacy of 16 Gy in two fractions of 8 Gy one week apart [31]. The response rate, duration of response, and survival were similar to those observed in patients treated with 30 Gy in 8–10 fractions in a previous publication from the same group [31,32]. Mild oesophagitis with dysphagia for solid foods occurred in 8 of 25 patients (35%) having the thoracic spine treated, and there were few skin reactions. Moreover, 16 Gy in 2 fractions 1 week apart reduced cost to the RT centre and patient burden due to fewer treatment visits. Back pain requiring high dose opioids occurred in 3 of 33 responders who initially did not have pain or had pain controlled by minor analgesics 4 to 13-months from RT. These patients with in-field relapse underwent a second palliative course of RT and did not develop reduced ambulation. Subsequently, a phase III, randomized controlled trial examining the efficacy of short-course 8 Gy $\times$ 2, one week apart *versus* split-course RT (5 Gy $\times$ 3; 3 Gy $\times$ 5) in the treatment of patients with SCC and a life expectancy $\leq$ 6 months was performed [21]. With 276 assessable patients, both RT courses were equally effective without severe side effects.

Soft tissue mass

Another relatively common clinical situation is complicated BM that present with a soft tissue mass or extra osseous component penetrating the cortical boundary. Patients in this population have traditionally had good response rates to RT [33]. A study of 30 patients with BM extending into soft tissues included 18 treated with RT but with no details concerning dose fractionation schedules [34]. In addition to these findings, our group evaluated the efficacy and safety profile of 16 Gy in 2 fractions of 8 Gy one week apart in complicated BM population cohorts [35]. In this phase II clinical trial, with 50 patients having poor performance status, 38 had an extra osseous soft tissue component, 18 needed post-surgical radiation, 3 had neuropathic pain, 3 had an impending fracture in a weight-bearing bone, and no patient had SCC [35]. At 2 months, 33 patients were alive (66%), four (12.5%) had a complete response and 12 (37.5%) had a partial response. A statistically significant improvement was seen in functional interference ($p = 0.01$) and psychosocial aspects ($p = 0.03$) of the BM22 QoL questionnaire. One patient required surgery for pathologic fracture, and another re-irradiation. 16 Gy in 2 fractions one week apart achieved satisfactory pain relief and safety results in patients with complicated BM [35]. It is important to point out the low survival rates in this group of patients, with a mean of 3.5 months after RT. This clearly supports shorter treatment and fewer visits, maintaining QoL in this group of patients.

One other study [33], identified five sites of soft tissue mass with no difference in response between varying fractionation schemes delivering doses which ranged from 20 to 60 Gy. This paucity of evidence has stemmed from the fact that much of the relevant literature is composed of case reports and small series [34]. As such, further research into this patient population and its appropriate management with RT is warranted.

Reirradiation

Reirradiation is more common after treatment with single fraction RT than in patients treated with multiple fractions RT [9]. These differences in the retreatment rate could represent a greater predisposition to repeat RT after single RT than a real need. In addition to the higher reirradiation rate, some studies suggest that patients treated with single dose RT could have more bone fractures and it has been argued that fractionated RT courses are preferable for patients with longer predicted survival [7,23,36–38].

In a large randomised study, the role of reirradiation was evaluated in 425 patients with painful BM comparing two fractionations, 8 Gy in 1 fraction and 20 Gy in five fractions. In the intention-to-treat analysis, after two months, the overall pain response rate using the Brief Pain Inventory Score was 28% in the 8 Gy group *versus* 32% in the 20 Gy arm ($p = 0.21$), and in the per-protocol analysis, it was 45% *versus* 51%, respectively ($p = 0.17$). Patients treated with 20 Gy compared with the 8 Gy arm reported more lack of appetite (66% *versus* 56%, $p = 0.011$) and diarrhoea (31% *versus* 23%, $p = 0.018$) [39].

Novel treatment paradigms in BM: systemic treatment, oligometastases, and local ablative technologies

Systemic anti-cancer therapy and oligometastases

Systemic anti-cancer treatment of metastatic cancer is becoming more targeted and precision-based with recent advances in molecular targeted therapies, novel hormonal agents and immunotherapy making chemotherapy no longer the only option for patients with advanced malignancies [15]. Selection of appropriate personalized systemic treatment strategies for metastatic disease is based on identification of actionable targets including EGFR, ALK, ROS1, and TREK-fusion in NSCLC; estrogen receptor, HER-2, CDK4/6, mTOR inhibition PIK3CA in breast cancer; RAS, BRAF, VEGF in colorectal cancer; androgen dependency in prostate cancer; VEGF, MET in renal cell carcinoma, VEGF in hepatocellular carcinoma, HER-2 in gastroesophageal cancer, and, more recently, PARP inhibitors for BRCA mutation carriers, and immune checkpoint inhibition of PD1, PDL1, and CTLA4 in various cancer types including melanoma, NSCLC, renal and head and neck cancers. For patients who are identified with BM, the decision whether to

proceed with or continue systemic therapy or to have local treatment is largely dependent on whether the patient is symptomatic with severe pain, with an imminent risk of fracture or spinal cord compression when RT or surgery should always be considered [15,21,31,32]. It is essential to assess and risk stratify the patient based on performance status, and restaging to evaluate the benefit from further systemic treatment, Fig. 1 [15].

The oligometastatic concept was first described in 1995 recognising a subset of patients with a more favourable prognosis due to limited metastatic disease where there might be a survival benefit with local ablative treatment, such as SABR and SRS, radiofrequency ablation (RFA) or surgery [40]. Recently, oligometastatic disease has been redefined as 1 to 5 metastatic lesions, with or without control of the primary tumour [41]. The theory behind giving metastases-directed ablative therapy to oligometastatic disease is based on the observation that in some patients further metastatic progression does not occur [42].

The *International Registry of Lung Metastases*, with data from 13 centres in Europe and 4 in North America collected data on 5,206 patients with lung metastases over five decades [43]. In cases with complete resection, the actuarial 5-year overall survival (OS) was 36%. A 5-year survival rate ranging from 28 to 58% for patients with colorectal hepatic metastasis treated with surgery is reported in four different studies with a total of 3733 patients [44]. The improved accuracy in image methods has enabled the early detection and the characterization of different types of oligometastases: induced oligometastatic disease, genuine oligometastatic disease (repeat or de-novo oligometastases); with additional classifications (synchronous, metachronous, oligorecurrence, oligoprogression, and oligopersistence) [45]. Therefore, local ablative therapies can delay change or use of systemic therapy, preserve patients' Qol, and improve disease-free survival, progression-free survival, and overall survival [46–50].

Oligometastases and local ablative therapy

Recently, in the phase II Comet trial, patients with oligometastatic disease, with 1 to 5 metastases and controlled primary tumours, were randomized to SABR to all known disease sites *versus* palliative RT if required [46]. In this study, bone was the second most common site of metastases, corresponding to one-third of metastases in the whole study (65/191 metastases). 35% (n = 45) of the patients in the experimental arm have BM *versus* 31% (n = 20) in the conventional RT arm [46]. Patients in the SABR group had longer median overall survival (41 *versus* 28 months, p = 0.09) and better progression-free survival (12 *versus* 6 months, p = 0.001) compared with the standard of care arm [46]. The ongoing COMET 3 and 10 trials have also included translational biomarkers: circulating tumour cells, peripheral circulating immune cells, and circulating tumour DNA [51,52].

Cohort studies of local treatments have demonstrated benefits in oligometastatic patients in specific cancer types. In the phase II STOMP trial, prostate cancer patients receiving local treatment (metastasectomy or SABR) had an improved 5-year hormone therapy-free survival of 34% *versus* 8% in the observation group [47]. This is similar to a single arm study reporting a 2-year hormone therapy-free survival of 48% with SABR in metastatic prostate cancer patients without previous androgen blockage with a local progression-free survival of 97% and 93% at 1 and 2 years, respectively [48]. In patients with non-resectable colorectal liver metastases, in the European Organization for Research and Treatment of Cancer (EORTC) 40,004 trial, the addition of local therapy to systemic therapy increased the median progression-free survival (PFS) to 16.8 months *versus* 9.9 months with systemic therapy alone [49]. At three years, the PFS rate with local treatment was 27.6% compared to 10.6% with systemic treatment alone (p = 0.025) [49]. The observed median OS was 5 months longer in the arm with local therapy compared with chemotherapy alone after a long-term median follow-up of 9.7 years [49].

A further study in stage IV non-small cell lung cancer (NSCLC) patients with oligoprogressive disease who received local ablative therapy for progressive or persistent metastases while receiving targeted, or immunotherapy showed survival rates that seem to show an improvement compared to patients in the literature who received systemic treatment alone [53]. The median time to

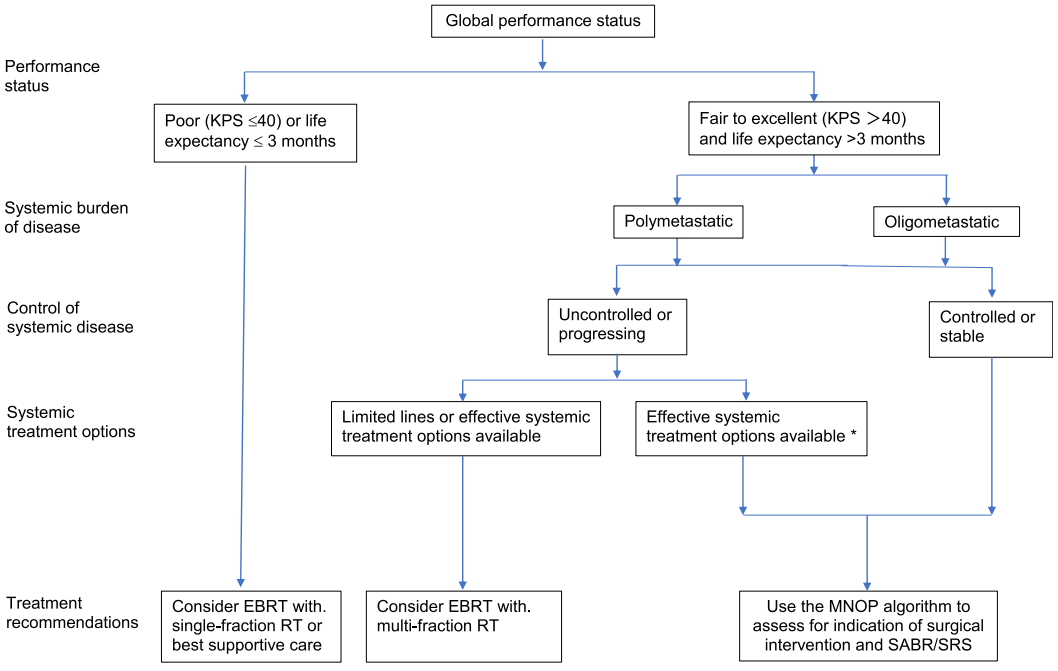

Fig. 1. Initial assessment algorithm for patients with bone metastases KPS = Karnofsky performance status. EBRT = external-beam radiotherapy. MNOP = mechanical, neurological, oncological, preferred treatment. * For select patients with effective systemic therapy treatment options, systemic therapy without use of radiotherapy might be appropriate.

therapy switch was 14 months for oligoprogressive disease patients compared to 8 months for polyprogressive disease patients [53]. Similarly a retrospective cohort study of oligometastatic NSCLC patients using local consolidative therapy in addition to systemic therapy, where 64% received platinum chemotherapy while 24% received angiogenesis inhibitor or targeted therapy, was associated with better survival ($p = 0.034$) [50]. Although evidence to support the concept of targeting oligoprogressive disease while continuing systemic therapy beyond progression is limited, it is increasingly practised in the real world clinical setting.

Ablative techniques for bone metastases

Stereotactic irradiation techniques like SRS and SABR enable administration of ablative doses of radiation to primary or metastatic tumours sparing the surrounding healthy tissues with a rapid fall of dose outside the target. The "ablative effect" associated with high dose radiation overcomes intrinsic tumour cell radioresistance and induces indirect effects, including vascular endothelial injury and immune activation [54]. While the ASTRO BM guideline suggests that SRS and SABR in BM should be limited to clinical trials [15], the National Comprehensive Cancer Network (NCCN) guideline recognizes that SRS and SABR may be preferred in three circumstances: reirradiation (to reduce RT dose in the spinal cord and other critical organs), oligometastatic disease (with the purpose of tumour ablation), and in radioresistant tumours (melanoma, sarcoma, renal cell, and hepatocellular carcinoma) [55]. In Table 1 and Table 2, the studies with different uses of such modalities and their outcomes are summarized [56–85].

A systematic review of SABR for BM analysed 38 studies evaluating pain response and 45 reporting local control. The local control rate was higher than 80% in most studies, and a >75% pain response was seen in more than half the studies with few high-grade toxicities [54]. In the largest study in this series, with *Patient Reported Outcomes* in 149 cases, there were 12 grade 3 events (fatigue, pain, gastrointestinal disorder, and diaphoresis); spinal myelopathy was not reported, and reported low-grade toxicities were nausea, vomiting, and temporary numbness and tingling [68]. Ten trials with 676 patients prospectively registered toxicity and reported a 0.03% rate of grade 3 or 4 toxicity ($n = 19$) [54]. In the 28 studies evaluating toxicity retrospectively, the rate of grade 3 or 4 toxicity was very low as well (5 cases in 2033 patients) [54]. The median survival in these studies (ranging, 8–47 months), is longer than observed in conventional RT phase 3 trials in BM (median, 7 months) suggesting patient selection [23,54].

A meta-analysis included 3237 patients with 4911 spinal oligometastases treated with SRS (43.8%), SABR (19.7%), or conventional RT (36.5%) [86]. SRS treatment was associated with increased 1-year local control compared with conventional RT (92.9% *versus* 81.0% respectively, $p = 0.007$), and there was no difference in local control between conventional RT and SABR (81.0 % *versus* 82.1%, $p = 0.86$) [86]. The overall grade 3–5 toxicity rate was low in all the groups, 0.4%, 0.2%, and none for SRS, SABR, and conventional RT, respectively. Nevertheless, SRS was associated with a higher risk of vertebral collapse fractures than SABR (19.5% *versus* 9.6%, respectively, $p = 0.039$) without an apparent dose effect [86]. In contrast another review found doses per fraction $\geq$ 20 Gy were associated with increased vertebral fracture risk [87].

A randomized phase II study of 55 patients with painful spinal BM, reported that treatment with SRS (24 Gy/1 fraction) produced a faster reduction in pain than conventional RT (30 Gy/10 fractions) [80]. A higher pain response at 6 months was also described, 73.7% with SRS *versus* 35% with conventional RT ($p = 0.003$); however, there were no differences in analgesic intake at 3 and 6 months) [80].

Another randomized phase II study showed higher pain control with SABR (24 Gy in 2 fractions) than with conventional RT (20 Gy in 5 fractions) [84]. At 3 months, the complete pain response rate was 36% (40/114) in the SABR arm *versus* 14% (16/115) in the conventional RT arm ($p < 0.001$). This difference persisted at 6 months, with 33% (37/114) complete pain response in the SABR group versus 16% (18/115) with conventional RT ($p = 0.004$) [84].

However, in the early results of the phase 2/3 RTOG 0631 study, SABR did not improve pain response in patients with one to three spinal BM compared to conventional RT [81]. 209 patients were treated with SRS (16–18 Gy) and 130 received conventional external RT (8 Gy/1 fraction) and there were no differences in pain scores at 3 months ($p = 0.99$). Other important outcome measures when using SRS or SABR are complete response in terms of metastatic disease control and a consequent survival improvement which have yet to be reported [81].

Comparison of single-dose SABR (24 Gy) with fractionated SABR (27 Gy in 3 fractions) found that single-dose SABR was associated with a lower local relapse rate at 2 and 3 years, 2.7% and 5.1%, respectively, compared with 9.1% and 22% with fractionated SABR ($p = 0.0048$) [85]. Furthermore, there was also a difference in progression with distant metastases in favour of single-dose SABR 5.3%, compared with 22.5% with SABR in 3 fractions in 3 years ($p = 0.010$) [85]. A consensus guideline has acknowledged the role of SABR after surgery in spine BM with tumours restricted to 1–2 vertebral levels, radioresistant disease, and previous RT [88].

Reports on nonspine bone metastases (NSBM) are limited. In a systematic review by Spencer *et al*, only 8 of the 57 reviewed studies included NSBM and only 2 studied a population consisting exclusively of NSBM patients [54]. There appears to be significant heterogeneity in the delivery of NSBM-SABR globally in terms of treatment technique and dose prescription. An expert consensus report on bone SABR, found complete agreement for a dose delivering a BED of $\leq$100 Gy_{10}, and more than half of the panelists selected dose fractionations that had a BED of 60 Gy_{10} [89]. The majority would de-escalate the dose for re-irradiation with SABR and in weight-bearing bones with significant cortical erosion [89]. The lower bone SABR dose compared to other conventional SABR sites such as liver and lung where a BED > 100 Gy_{10} would usually be recommended reflects effective local control with lower doses and concern over RT-induced fracture. Single institution study have reported local control rates of 95% and 87% at 6 months and 24 months using SABR 30–35 Gy/5fr for NSBM, respectively [90]. Another study used a wider range of SABR doses (15 Gy/1fr–50 Gy/5fr) and reported a 1- year LC rate of 92% [91].

Immunotherapy and SABR

Programmed death ligand 1 expression level is known to be correlated with response to immune checkpoint inhibitors (ICI) with PD1/PDL1 inhibitors. RT may be able to induce PDL-1 expression, improve response to immune checkpoint inhibition, and prevent development of resistance to immunotherapy [92–94]. In a single arm phase 2 trial with oligometastatic ($\leq$4 metastases) NSCLC patients, the use of pembrolizumab following a local ablative treatment to all tumour sites was associated with a significant improvement in the median progression-free survival of 19.1 *versus* 6.6 months when compared with historical data ($p = 0.005$) [92].

A small nonrandomized observational study in patients with early-stage NSCLC, treated with surgery ($n = 13$) or SABR ($n = 10$), demonstrated that SABR induces systemic blood T-cell activation in a major subgroup of patients [93]. Moreover, a study of 37 prostate cancer patients with oligometastatic ($\leq$3 metastases) treated with SABR, reported that an increase in the CD8+ tumour-reactive cells decreased the risk of local progression ($p = 0.032$) [94]. In contrast, an increase in the CD8+ T central

Table 1
Stereotactic ablative radiotherapy (SBRT) trials and type of study in bone metastases patients.

Author, year [Ref.]	SABR use	Study Type	Pain Response (%)	Local Control	Number of Patients	Total Dose (Gy)	Number of Fractions	Device	RT Prescription Parameters
Gerszten, 2005 [56]	POS	Prospective Single arm	92	-	26	mean 18 (16 to 20)	1	CyberKnife	80% isodose line
Gagnon, 2007 [57]	RIR, CCRT	Retrospective Matched-pair analysis of historical controls	-	-	35	21–28	3–5	CyberKnife and Linac	Not mentioned
Choi, 2010 [58]	RIR	Retrospective	65 (considering patients presenting with pain)	73 (1y)	42	median 20 (10–30)	median 2 (1–5)	CyberKnife	77% isodose line (median) (range, 68–88%)
Staehler, 2010 [59]	RRT	Retrospective	-	94.1(1y)	55	20 median (19–20)	1	CyberKnife	70% isodose line (median) (range 50–85%).
Garg, 2011 [60]	RIR	Prospective	-	76 (1y)	59	27–30	3–5	Linac	80% to 90% of the target volume received the prescription dose
Mahadevan, 2011 [61]	RIR	Retrospective	65 (1 month after SBRT)	93 (last visit)	60	24–30	3–5	CyberKnife	Mean prescription isodose 79% range(68–90%)
Nikolajef, 2011 [62]	RIR	Retrospective	significant reduction in VAS score of patients with pain (2 months)	88 (1y)	54	median 18 (10–28)	1	CyberKnife	Median prescription isodose line 70% (range 50–80%)
Chang, 2012 [63]	RIR, PRI	Retrospective	81–89 (1y)	Retreatment: 81 (1y) Initial RT 89 (1y)	185	Retreatment: 14.7–26.5 Initial RT: 16.6–23.2	1	CyberKnife	Retreatment: 78.3 % isodose line Initial RT 79.3 % isodose line
Heron, 2012 [64]	PRI	Retrospective	88 MF vs 100 SF	96 MF vs 70 SF (2y)	228	MF: 20.6 (9–26.3) SF: 16.3 (6–20) 1	MF: 3–5 SF: 1	CyberKnife	MF: 80% isodose line (range 70%–95%) SF: 72% isodose line (range 50%–85%)
Hunter, 2012 [65]	CCRT, RRT	Retrospective	CRT: 68 - SBRT:62 (overall)	-	110	8–30	1–10	Linac	CRT: prescribed to a depth, or the isocentre SBRT: not mentioned
Jahanshahi, 2012 [66]	RRT, OLI	Retrospective	-	72–100 (1y)	50	mean 24.1 (7.7–54)	1–5	CyberKnife	Mean prescription isodose 78.7%
Massicote, 2012 [67]	POS, RRT	Retrospective	Median improvement on VAS was 6 points (5 months)	70	10	median 24 (18–35)	1–5	Linac	80–90% of CTV coverage
Wang, 2012 [68]	PRI, RIR, POS	Prospective	Increase in patients without 26.2 vs 53.9 (6 months)	80.5	149	27–30	3	Linac	Not mentioned
Al-Omair, 2013 [69]	POS, RRT	Retrospective	-	84 (1y)	80	median 24 (18–40)	median 2 (1–5)	Linac	Median CTV V80 in 90% of the patients
Laufer, 2013 [70]	POS, RRT	Retrospective	-	83,6 (1y)	186	18–36	1–6	-	Not mentioned
Muacevic, 2013 [71]	OLI, RRT	Prospective	-	95 (1y)	40	median 20 (16.5–22)	1	CyberKnife	Median peripheral isodose 70% (60–80)
Folker, 2014 [72]	RRT, OLI	Retrospective	-	87.9 (1y)	88	18–36	1–6	Linac	Median prescription D95% coverage 95% of PTV
Amini, 2015 [73]	RRT, CCRT	Retrospective	74.9 SBRT, 39,9 Conv (1y)	74.1 S – 45,1C (1y)	46	8–40	1–12	Linac	Not mentioned
Colaco, 2015 [74]	OLI	Retrospective	-	89 (1y)	78	10–17	1–3	Linac and Gamma Knife	Not mentioned
Thibault, 2015 [75]	RIR	Retrospective	-	81 (1y)	40	20–35	1–5	Linac	Aimed to cover > 80% of the PTV minus the CNT with 95–100% dose.
Ghia, 2016 [76]	RRT, POS	CRT	-	82 (1y)	43	24–30	1–5	Linac	isodose was normalized to the isocenter and the dose prescribed to the volume included by the 90% isodose line

Table 1 (*continued*)

Author, year [Ref.]	SABR use	Study Type	Pain Response (%)	Local Control	Number of Patients	Total Dose (Gy)	Number of Fractions	Device	RT Prescription Parameters
Sohn, 2016 [77]	CCRT	Retrospective	Post-treatment VAS scores were lower in both groups	32 conv, 59 SBRT (1y)	56	Mean 31–35	Mean 4–10	CyberKnife and Linac	Tumor volume covered by the prescription dose was more than 90% (mean, 96%).
Ursino, 2016 [78]	OLI	Retrospective	-	90.2 (1y)	40	24–27	1–3	Linac	Not mentioned
Mehta, 2018 [79]	POS, PRI, OLI, RIR	Retrospective	-	84% (1y)	83	median 24 (14–44)	median 3 (2–5)	CyberKnife	Plans were optimized to try to keep the prescription isodose line ≥ 80%.
Sprave, 2018 [80]	CCRT	Prospective	52,6 SBRT vs 10 Conv VAS complete response (6 months)	-	55	24–30	1–10	Linac and TomoTherapy	SBRT PTV covered by 80% isodose.
Ryu, 2019 [81]	CCRT	Prospective	No difference in pain response (3 months)	-	339	8, 16–18	1	-	Not mentioned
McGee, 2019 [82]	PRI, RRT, POS	Retrospective	93 in patients with pain	41 vs 85 (1y)	41/96	14–18	1	Linac	dose prescribed to the 100% isodose line, and normalization values ranged from 90% to 113.5%.
Nguyen, 2019 [83]	CCRT	Prospective	77 SBRT, 46 conv (9 months)	100 vs 90.5 (1y)	160	12–16, 30	1, 10	Linac	Mixed radiotherapy techniques from conventional (2d) to SBRT.
Sahgal, 2020 [84]	CCRT	Prospective	33 SBRT vs 16 conv (6 months)	69 vs 75	229	20–24	1–5	-	Not mentioned
Zelefsky, 2021 [85]	PRI, OLI	Prospective	-	94.2 vs 78 (3y)	117	21–24	1–3	Linac	100% isodose line

Abbreviations: POS, postoperative SBRT; CCRT, comparing with conventional RT; RIR, reirradiation; OLI, bone and or visceral oligometastases; PRI, primary treatment, and RRT, radioresistant tumors; CTV, the clinical target volume; PTV, planning target volume; CNT, critical neural tissues.The selection criteria data for each trial is available in Table 2

memory cells, which may result in a tumour-bearing state limiting tumoricidal cytotoxic activity, was connected to the risk of death (p = 0.033) [94]. These observations strengthen the need to perform clinical trials combining SABR with immunotherapies [93].

Toxicities of combining SABR with systemic treatment

Toxicity data for concurrent treatment of SABR and systemic treatment is limited and mostly reported for cranial SABR. Concurrent treatment is mostly well tolerated in cranial SABR, but higher rates of severe toxicity were observed when combined with BRAF-inhibitors [53]. In a systematic review, the authors reported a scarce literature on extra-cranial SABR but a potential risk of increased toxicity when SABR is combined with EGFR-targeting tyrosine kinase inhibitor, and bevacizumab, which was not observed for cranial SRT [53]. Patients receiving SABR targeting the liver and concurrent use of sorafenib also seemed to experience more toxicities [53].These findings concurred with a systematic review, which found increased toxicities when RT is combined with bevacizumab, cetuximab, and tyrosine kinase inhibitors [95].

Although several trials have shown that the addition of antiangiogenic agents to conventionally fractionated radiation therapy is well tolerated, other reports have demonstrated increased luminal gastrointestinal toxicity with the combination, especially in patients on anticoagulation [96–101]. Bevacizumab appears to be more associated with GI toxicity than some of the other agents such as sunitinib and sorafenib [102]. It is believed that SABR is more likely to result in GI mucosal injury by preventing normal tissue recovery in the post-SABR period and thus make SABR-related toxicity more likely [103]. EGFR and ALK tyrosine kinase inhibitors are generally safe, but caution is required around potential lung toxicity with interstitial pneumonitis while on tyrosine kinase inhibitors, especially when the concomitant RT volume includes lung [104].

In metastatic breast cancer, BM are commonly seen in hormone receptor positive tumours and the treatment of choice would be hormonal therapy such as tamoxifen, aromatase inhibitor, or fulvestrant in combination with CDK4/6 inhibitors (ribociclib, palbociclib or abemaciclib) [105–108]. For patients with previous GI toxicity using CDK4/6 inhibitors, RT should be highly conformed to spare the GI mucosa [109]. For HER-2 positive breast cancer patients, anti-HER2 agents such as trastuzumab, pertuzumab, T-DM1 and tyrosine kinase inhibitors such as lapatinib, neratinib and tucatinib are generally safe when given with RT and may contribute to a radiosensitizing effect on tumour cells [110–112]. Antiandrogens used in prostate cancer such as abiraterone, and enzalutamide are found to be generally safe when given with RT and may contribute to a radiosensitizing effect on tumour cells [113,114].

The use of immune-checkpoint inhibitors with ablative RT is generally found to be safe. No difference in adverse events was noted among patients who received combination therapy compared to those who received either modality alone [115–122].

In castration resistant prostate cancer patients who received at least one course of bone-directed RT with 8 Gy in one fraction with or without Ipilimumab had no adverse effects [116]. In combination treatment, dual immune checkpoint inhibitors (ICPI) using a PD1/PDL1 inhibitor with a CTLA4 inhibitor, combinations with chemotherapy or anti-VEGF agents are likely to be more toxic when used concomitantly with SABR, especially anti-VEGF agents and precautions need to be taken if triple modalities are to be given together [123]. Using combination immunotherapy with nivolumab and ipilimumab increased toxicity is reported with more than 45% grade 3 and 4 immune-related adverse events (irAEs) [123,124]. IrAEs can generally be managed using corticosteroids from 0.5 to >2 mg/kg/day and other immunosuppressants if the

AEs do not resolve with steroids. It is controversial whether corticosteroids, commonly given before RT to the bone especially for malignant cord compression, would dampen ICI efficacy. Adjustment of schedules and doses of ipilimumab were found minimise irAEs using reduced dose and extended dosing intervals to every 6 or 12 weeks [125,126].

Interventional radiological local ablative techniques

Thermal ablation consists of several techniques, the most commonly used include radiofrequency, cryotherapy, laser, and microwave thermal ablation [127].In Dupuy et al's study, CT-guided RFA of BM effectively reduced pain at 1 and 3 months post-treatment. Adverse events related to RFA occurred in approximately 5% with neurological damage and neuropathic pain related to heat-related damage to nerves adjacent to the ablated region [128]. RFA can be combined with cement injection to add value in pain relief and bone stabilization at various skeletal sites including the vertebral bodies and long bones. [127]. The effectiveness of pain palliation is related to the size of the lesion [128]. Tumour local control can be achieved in 70–80% at 1 year and multiple lesions can be treated in the same session avoiding ionizing radiation [129,130].

A newer ablative technique includes magnetic resonance imaging-guided high-intensity focused ultrasound (HIFU), also known as MR imaging-guided focused ultrasound surgery (MRgFUS). In a phase 3 trial, with 147 patients, self-reported pain score had a response rate of 64% compared with 20% for placebo [131]. The most common adverse effect was sonication pain occurring in 32.1% of MRgFUS patients. Other adverse events include pathological fractures in two patients, third-degree skin burn in one patient, and neuropathy in one patient. Most AEs were short-lived and resolved in 60.3% of patients on the first treatment day [131]. MRgFUS can be used as salvage therapy in patients not suitable for re-irradiation.

Embolization is a palliative treatment option for BM either alone or in combination with other treatments specifically for hypervascular tumors such as renal cell carcinoma, thyroid cancer, and hepatocellular carcinoma demonstrating effective control of pain and neurological symptoms [132–134]. One report of selective and super-selective embolizations in 243 patients with bone metastases achieved a pain reduction in 97% of patients with a mean duration of pain relief for 8.1 month [135]. Embolization can also be used to devascularize the tumour before thermal ablation to reduce the heat/cold-sink effect of ablation [136].

Bone modifying agents

Bone modifying agents are systemic agents that can be used to treat osteoporosis, or in the case of BM to control pain and prevent skeletal-related events (SRE). Bisphosphonates and denosumab are commonly used in clinical practice. In the adjuvant setting, the EBCTCG study demonstrated that adjuvant bisphosphonates reduced the rate of breast cancer distant recurrence, bone recurrence, and breast cancer mortality, especially in postmenopausal women [137].

In the setting of BM, denosumab has been found to be at least non-inferior compared to zoledronic acid in delaying SRE in solid tumours and multiple myeloma in various studies [138–140]. Some early studies have even demonstrated an overall survival benefit, but phase 3 randomized trials have failed to confirm this [141,142].

In EGFR mutated adenocarcinoma of lung, treatment of osteolytic lesions using tyrosine kinase inhibitors has shown accelerated re-ossification of lytic lesions and together with bisphosphonates, could improve overall survival [143,144]. When an EGFR TKI was omitted, there was an increased and earlier risk of SRE which could ultimately impact survival [145]. In the age of immunotherapy, beyond its supportive role, bone is a haematopoietic organ consisting of lymphoid tissue that modulates the immune system. Metastatic NSCLC patients who received nivolumab with bone metastases were found to have a lower overall response rate, shorter progression-free-survival and overall survival compared to patients who did not have BM [146]. There are several studies that have found the combination of ICI with denosumab, a RANKL inhibitor, can enhance objective response to more than 50%, and prolong PFS and OS by possibly priming the tumour microenvironment to respond to RANKL blockade and improving antitumour activity [147–149].

Physical activity, exercise, and rehabilitation in patients with BM

When treating pain related to BM, physical activity, exercise, physical medical modalities (eg. transcutaneous electrical nerve stimulation) are often perceived as contraindicated due to possible pathological fractures and spinal cord compression [135]. Regular physical activity, exercise and other physical modalities should be incorporated into the multidisciplinary and multimodality treatment of BM. Modalities increasing local blood flow like ultrasound therapy, thermotherapy, massage, and various electrotherapy options should not be performed near the tumour site [136]. Physical activity and exercise should be encouraged aiming to improve muscle strength, endurance capacity, sensorimotor functions, flexibility, and functional status [136]. Such rehabilitation programmes should be individually tailored and adapted to maintain the patient's condition and to minimise risks [136]. A review of studies that prescribed exercise for patients living with metastatic cancer reported good patient acceptance, tolerance, and adherence [150]. Statistically significant and clinically meaningful improvements were found in exercise behaviour, muscle mass, muscle strength, and endurance capacity [150]. Most importantly, few adverse events related to exercise interventions were reported [150,151]. A controlled study evaluated the efficacy and safety of an exercise programme consisting of aerobic, resistance, and flexibility exercise in prostate cancer patients with bone metastases and found patient-reported improvement in physical functioning and lower body muscle strength with no complications or increase in skeletal pain [151].

Patient autoregulation during exercise programmes allows self-determination of exercise capabilities according to their fitness [150]. It is important to note when prescribing resistance exercise the location of BM to ensure affected regions are not targeted and mechanical and sheer force at areas of metastases are minimized [150].

For patients with stable BM, physical activity using isometric exercise can maintain painless mobility. Braces can be used to stabilize the vertebral column and peripheral joints, either for mechanical stabilization after surgery or as a preventive measure for unstable bone metastases that are medically or surgically inoperable in combination with other treatment modalities such as systemic anti-cancer treatment, radiotherapy, and bone modifying agents for the treatment of bone metastases [135].

According to the American College of Sports Medicine, if patients show no contraindications for active exercise, regular physical activity includes: 150 min per week of moderate intensity or 75 min per week of vigorous intensity activity or an equivalent combination and muscle strengthening activities of at least moderate intensity for at least 2 days per week for each major muscle group with stretching of major muscle groups and tendons [152].

Other areas that may be important during the rehabilitation process include adequate patient and carer information and education in relation to physical activities; BM specific nutritional programmes to maintain muscle mass, and psychological assessment for patients becoming newly disabled [136].

Discussion

The decision making process in the management of BM remains complex. Several publications have described strategies to guide clinicians on the management of spinal metastases including the NOMS framework, the LMNOP system, and the integrated multidisciplinary algorithm by the *International Spine Oncology Consortium group* [153–155]. The initial assessment algorithm for patients with spinal metastases evaluates patients based on 4 aspects: performance status, systemic burden of disease, control of systemic disease, and available systemic treatment options and their efficacy which would stratify patients according to prognosis, Fig. 1 [155]. Another important factor to consider in the patient stratification of available treatment options is resource, which includes the institution, the patient and their carer, and financial resources which may limit available treatment options. If the patient satisfies all 5 areas required to proceed with aggressive surgical, RT, or systemic treatment, then the MNOP (Mechanical, Neurological, Oncological, Preferred treatment) algorithm should be considered [155]. The algorithm proposed by the *International Spine Oncology Consortium* can also be applied in nonspine BM including complicated bone metastases using the same principle but instead of using the spinal instability neoplastic score, one would assess mechanical stability of the bone metastases by using the Mirel's score or other factors such as the size of the soft tissue mass adjacent to the BM to review a patient's risk of pathological fracture and whether surgical intervention may be indicated.

It is important to note that various prognostic models have been developed to estimate patient prognosis and survival from spinal metastases [156–161]. However, these models are seldom used in clinical practice because of limited accuracy when applied to the individual.

It is essential to consider that several of the trials assessing conventional RT for simple BM lack detailed radiological and clinical details relating to factors leading to complications, and the evaluation of local control with serial imaging is rarely used [17,18]. Furthermore, few of these trials evaluated patient performance status, and heterogeneity in the assessment of toxicity makes comparison across studies difficult [17,18].

Despite the advantages in time, convenience, and cost-effectiveness, the use of single-fraction RT with conventional dose remains low even in patients with uncomplicated BM [10,11]. Most BM phase 3 trials were performed prior to the development of modern ablative techniques like SABR and the introduction of improved systemic therapy including immunotherapy, targetted therapy, and radiopharmaceuticals [15].

Furthermore, there is a paradigm shift in systemic anticancer treatment with the increasing use of immune-checkpoint inhibition in patients with metastatic cancer. [147–149]. Clinical and pre-clinical data demonstrates that SABR is also able to modulate the immune system shown in circulating immune cells in peripheral blood [93,94]. In patients with oligometastases, local ablative therapies may improve disease-free survival [46–50]. SABR in BM appears to be safe, with good rates of pain and local control, including fast relief of the pain, and with a small probability of severe complications [54,86,87]. In spinal BM, SABR with single doses higher than 20 Gy can increase vertebral fracture risk [87]. A good dose–response relationship was recognized with 12–16 Gy in a single fraction particularly in radioresistant tumours [87]. However, the occurrence of three deaths (4.5%) in the interventional arm in the SABR-COMET study highlights the need for caution using high doses per fraction with SABR in patients with oligometastatic disease [46].

BM studies should describe pain scores, low and high-grade toxicities, at baseline and regular intervals, with standardized methods, including physician and patient-reported outcomes measurements. QoL and cost effectiveness also need to be studied in future studies. In addition, trials in BM and oligometastases should analyze overall survival, disease-free and progression-free survival, survival without systemic therapy, local control with serial images, and also study the benefit of combined therapy. Like SABR-COMET 3 and 10, future SABR trials should investigate translational biomarkers to define oligometastatic disease better, identify new predictors of prognosis, and improve understanding of the effect of SABR in the immune system [51,52]. Data from additional clinical trials in progress is available in Table 3.

Most systemic therapies appear to be safe to use in combination with palliative RT, but some drugs deserve further research. For patients with previous GI toxicity using CDK4/6 inhibitors, radiotherapy should be highly conformed to spare the GI mucosa [109]. Antiangiogenic agents can increase GI toxicity, and special attention is required in anticoagulated patients treated with SABR [100–103]. Tyrosine kinase inhibitors used concomitantly with radiotherapy may increase the risk of pneumonitis [104]. Combination treatment with different types of drugs like dual ICPI, ICPI with chemotherapy, and ICPI with anti-VEGF are expected to be more toxic, particularly with SBRT [123].

Conclusion

In conclusion, BM is a common complication in patients suffering from cancer and it is estimated that around 50% of patients develop BM in the course of their disease. Complications, such as pain and fracture lead to poor QoL and reduce survival [1–3]. Over recent years, various advances in the management of BM have been proposed to optimise management in the light of greater understanding of the mechanisms involved. The growing use of systemic therapies may play an important role in the future care of this group of patients and further well-designed, randomised controlled trials are still needed to provide evidence to guide the best care for our patients with bone metastases.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.07.022.

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