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Multidisciplinary Treatment of Non-Spine Bone Metastases: Results of a Modified Delphi Consensus Process

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ABSTRACT

Purpose: Local treatment for bone metastases is becoming increasingly complex. National guidelines traditionally focus only on radiation therapy (RT), leaving a gap in clinical decision support resources available to clinicians. The objective of this study was to reach expert consensus regarding multidisciplinary management of non-spine bone metastases, which would facilitate standardizing treatment within an academic-community partnership.
Methods and Materials: A multidisciplinary panel of physicians treating metastatic disease across the Memorial Sloan Kettering (MSK) Cancer Alliance, including community-based partner sites, was convened. Clinical questions rated of high importance in the management of non-spine bone metastases were identified via survey. A literature review was conducted, and panel physicians drafted initial recommendation statements. Consensus was gathered on recommendation statements through a modified Delphi process from a full panel of 17 physicians from radiation oncology, orthopaedic surgery, medical oncology, interventional radiology, and anesthesia pain. Consensus was defined a priori as 75% of respondents indicating "agree" or "strongly agree" with the consensus statement. Strength of Recommendation Taxonomy was employed to assign evidence strength for each statement.
Results: Seventeen clinical questions were identified, of which 11 (65%) were selected for the consensus process. Consensus was reached for 16 of 17 answer statements (94%), of which 12 were approved after Round 1 and additional 4 approved after Round 2 of the modified Delphi voting process. Topics included indications for referral to surgery or interventional radiology, radiation fractionation and appropriate use of stereotactic approaches, and the handling of systemic therapies during radiation. Evidence strength was most commonly C (n = 7), followed by B (n = 5) and A (n = 3).
Conclusions: Consensus among a multidisciplinary panel of community and academic physicians treating non-spine bone metastases was feasible. Recommendations will assist clinicians and potentially provide measures to reduce variation across diverse practice settings. Findings highlight areas for further research such as pathologic fracture risk estimation, pre-operative radiation, and percutaneous ablation.

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Introduction

Bone metastases are common among patients with metastatic disease, and often cause pain and functional impairment [1]. While comprehensive multidisciplinary guidelines exist for spinal metastases [2], national guidelines for the management of non-spine bone metastases have traditionally focused on radiation therapy (RT) to palliate pain, and surgical intervention and bone modifying agents to treat or prevent pathologic fractures [3,4]. A recent review showed the most common locations for these lesions include the hip/pelvis, ribs, shoulder, and femur and comprise 46% of all bone metastases treated in a tertiary radiation oncology center [5]. However, as systemic therapies have evolved and options for local therapy have increased, the utility of existing guidelines in routine care is increasingly limited. With this growing complexity, variation in practice patterns by clinical setting has been observed, demonstrating possible opportunities to standardize practice and improve outcomes [6].

In this study, we leveraged a community-academic partnership (in which the main academic center has a dedicated multidisciplinary team for managing bone metastases) to develop consensus recommendations that build on existing guidelines and would be applicable in multiple practice settings. We hypothesized that consensus on key multidisciplinary topics in the management of non-spine bone metastases would be feasible and provide the foundation for a future prospective study aimed to improve patient access to high-quality, patient-centered metastatic cancer care across diverse practice settings.

Methods

Consensus clinical setting and panel composition

The Memorial Sloan Kettering (MSK) Cancer Alliance is a community-academic partnership between MSK (a tertiary academic center) and community-based hospitals (Hartford HealthCare Cancer Institute, Lehigh Valley Cancer Institute, and Miami Cancer Institute at Baptist Health South Florida). MSK founded this Alliance with the goals of a) rapidly bringing the newest standards of care into community-based cancer practice settings and b) increasing patients' access to clinical trials in their local areas. MSK is unique in having radiation oncologists specializing in metastatic disease and co-leading both multidisciplinary clinics and a weekly tumor board [7].

The current study involved clinicians from multiple disciplines managing patients with non-spine bone metastases across the community-academic partnership. The *clinical steering committee* was comprised of 2 radiation oncologists, one orthopaedic surgeon with fellowship training in orthopaedic oncology, and one interventional radiologist, all from the main academic center. The *initial expert panel* (for Phase 1 to identify topics for consensus) was comprised of 7 radiation oncologists, 2 orthopaedic surgeons with fellowship training in orthopaedic oncology, and one interventional radiologist and represented the MSK Cancer Alliance community-based partners. The *full expert panel* (for Phase 2 consensus voting) consisted of 9 radiation oncologists, 2 surgeons with fellowship training in orthopaedic oncology, 2 medical oncologists, one interventional radiologist specializing in oncologic procedures, one anesthesia pain specialist, and one medical physicist. Full panel participation by practice location included: MSK (n = 11), Miami Cancer Institute at Baptist Health South Florida (n = 2), Lehigh Valley Cancer Institute (n = 2), and Hartford HealthCare Cancer Institute (n = 1).

Consensus process

We conducted a modified Delphi consensus process between March 2020 and March 2021. This iterative process leverages a systematic progression of repeated rounds of voting to determine expert group consensus where high-level evidence may be lacking and opinion is important [8]. We incorporated specific Delphi procedures including de-identified response, iteration and controlled feedback, and summary statistics to elicit and refine group judgement, in keeping with established methods [9]. Modifications to the Delphi included group meetings at the end of each Round (as documented previously through "Estimate-Talk-Estimate" [10] and pre-specifying the recommendation agreement threshold. (See Fig. 1 for a process schema). We outline a 2-phase process for identifying topics then refining consensus recommendations, similar to a prior modified Delphi [11].

Phase I: Identify Topic Areas for Consensus

- A. Review existing clinical practice guidelines
- B. Select potential topic themes for consensus
- C. Construct clinical question items

Clinical Steering Committee (n=4)

- D. Rate importance of clinical question items
- E. Select clinical questions for further development
- F. Conduct literature review 📚
- G. Draft initial question and answer (Q&A) statements

Initial Expert Panel (n=10)

Phase II: Refine Consensus Recommendations

- A. Recruit full panel of experts
- B. Administer Round #1 Q&A statements
- C. Collect, aggregate, and analyze results
- D. Report Round #1 results to expert panel
- E. Revise Q&A statements
- F. Administer Round #2 revised Q&A statements
- G. Conduct additional rounds until 75% agreement

Full Expert Panel (n=17)

- H. Strength of Evidence grading

Clinical Steering Committee (n=4)

Survey to identify topic themes

Steering Committee   Full Expert Panel

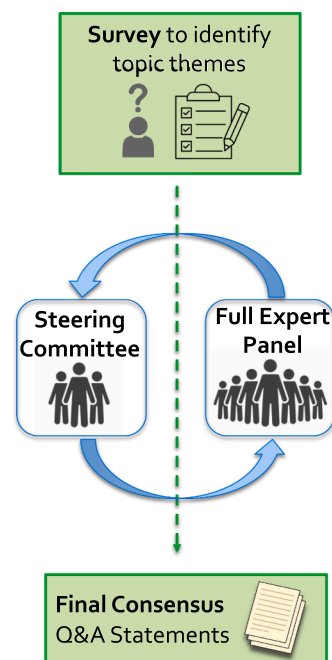**Final Consensus** Q&A Statements

Fig. 1. Schematic of the consensus process. 2 rounds of the modified Delphi process were required to reach consensus on 15 question/answer statements.

Phase 1: Identify topic areas for consensus

The clinical steering committee first conducted a review of existing clinical practice guidelines to identify potential gaps in available recommendations. Common clinical questions warranting multidisciplinary input in the management of non-spine bone metastases were identified. An online survey was distributed to multidisciplinary physicians across the MSK Cancer Alliance, requesting respondents rank the relative importance of each question on a 5-point Likert scale from "Not important" to "Essential." (See Supplemental Survey for instrument) The results of this survey were summarized by the clinical steering committee and presented to the initial expert panel in a meeting held on Zoom. Questions were selected for further development based on importance rating by panel participants and perceived feasibility of reaching consensus. Those with a median score of 5 ("Essential") were automatically advanced to the next step of the consensus process.

A literature review included references in PubMed published since January 1, 2010. Search terms specific to each previously identified question were drafted, using both MeSH terms and text (Supplemental Text). Exclusion criteria were non-human studies, publication in a language other than English, and studies conducted using subjects 18 years of age or younger. Based on these search terms, 1498 published articles were identified. Titles were screened (NM and KL) for exclusion criteria and relevance to the questions. A total of 90 primary articles were identified and summarized in tables that were then provided to 1–2 assigned expert(s) from the panel would drafted initial consensus answer statements (See Supplemental Draft Statement for an example clinical question and answer statement worksheet with evidence summary). Initial drafts were reviewed by the clinical steering committee who also had to approve any proposed modifications to the questions (including additional questions).

Phase 2: Refine consensus recommendations and grade evidence strength

Once preliminary question and answer statements (recommendations) were drafted, the full expert panel was recruited. We initiated Round 1 of voting by the full expert panel regarding their level of agreement or disagreement with each preliminary answer statements using a 5-point Likert scale from "strongly disagree" to "strongly agree," and were asked to provide comments. Voting was done individually via an online survey and results were de-identified. Modifications were proposed by the steering committee after each round of voting and presented to the panel in a Zoom meeting. Round 2 voting proceeded and the process continued until 75% of panel members "agreed" or "strongly agreed" with the statement, which was specified a priori.

The Strength of Recommendation Taxonomy (SORT) was employed to grade evidence strength [12]. The literature supporting the consensus recommendations was reviewed in duplicate and strength of recommendation was assigned (EFG, JTY), with any discrepancies between the two reviewers resolved by a third (NM).

Results

In Phase 1, 17 clinical questions were identified, of which 5 questions (29%) obtained a median importance score of "essential" and were automatically advanced to the next phase of consensus. These questions addressed complex case scenarios warranting multidisciplinary discussion, indications for surgical stabilization and *peri*-operative radiation fields, and radiation fractionation and indications for Stereotactic body radiation therapy (SBRT) (See Supplemental Table for details). The initial expert panel selected additional questions such that 11 total clinical questions (59%) proceeded for further development. One question regarding radiation margins was omitted due to recent publication of an international survey on the topic [13]. In the drafting stage, the following changes were approved by the steering committee and resulted in a final list of 12 questions: 1) one question added with

approval by the steering committee: "How important is the determination of treatment intent for patients undergoing local therapy for non-spine bone metastases?"; 2) Two questions regarding radiation fractionation (pain and oligometastases) were collapsed into a single question; 3) Interventional radiology techniques were split into 2 questions.

In Phase 2, 17 total physicians were recruited (as described in Methods). Answer statements were drafted and amended in response to Round 1 voting and feedback from the full panel, including splitting the systemic therapy recommendations into 5 separate statements for voting, for a total of 16 statements. Twelve of 17 (71%) statements were approved in Round 1 with the pre-specified 75% threshold for agreement, and 4 statements (24%) were approved in Round 2. Consensus could not be reached on standardizing normal organs contoured for radiation avoidance. The final set of clinical questions and answer statements are presented in Table 1. Evidence strength was most commonly rated as C (n = 7), followed by B (n = 5), and A (n = 3). A narrative summary of the evidence supporting each consensus recommendation is presented here.

Topic 1: Treatment intent

In the context of treatment for metastatic disease, the understanding of prognosis is important to how patients make decisions about future treatments and enrollment in hospice [14,15]. However, patients and family members' understanding of treatment intent and prognosis in the setting of advanced cancer is often inaccurate [16–19]. To ensure that patients have the information necessary to make informed decisions, treatment intent ought to be clearly specified when initial recommendations are made for patients with bone metastases.

Topic 2: Reporting of performance status

Performance status has been shown in both retrospective and prospective studies to correlate with survival for patients with advanced cancer [20–24]. In one study, Karnofsky Performance Status (KPS) alone was shown to have a stronger correlation with survival than clinical predictions made by oncologists [25], though this result has not been consistent [26]. The performance status scale proposed by the Eastern Cooperative Oncology Group (ECOG) has also been consistently shown to correlate with survival [27].

Topic 3: Definition and treatment of uncomplicated bone metastases

A definition of uncomplicated bone metastases has previously been proposed to include lesions which are painful, and unassociated with impending or existing pathologic fracture, and unassociated with existing spinal cord or cauda equina compression [28]. In addition to the complicated lesions identified previously, we chose to consider metastases with prior local therapy as complicated, as there are often different treatment considerations in the recurrent setting.

Radiation therapy is effective in alleviating pain for 60% of individuals with bone metastases and provides complete pain relief for about 25% of patients, with low rates of toxicity [29]. First-line RT is supported by high-level evidence from the meta-analysis of multiple randomized controlled trials and consensus guidelines from multiple professional organizations [3,30,31].

Topic 4: Indications for multidisciplinary review

A retrospective analysis of patients presented at the MSK non-spine bone metastases tumor board over a 3-month period (n = 42) revealed that 83% of the patients were presented for the four reasons listed in Table 1. Multidisciplinary discussion is also beneficial for individuals with symptoms that may or may not be caused by metastases, when there is uncertainty over the origin of a patient's pain or whether it is mechanical in nature. Lastly, while metastasis-directed radiation

Table 1

Question and answer statements for each clinical question in the treatment of non-spine bone metastases. % Agreement represents the percentage of study group members indicating "Agree" or "Strongly Agree" with the statement.

Question	Answer	% Agreement	Strength of Recommendation
1. How important is the determination of treatment intent for patients undergoing local therapy for non-spine bone metastases?	All patients undergoing local therapy for non-spine bone metastases should have treatment intent, generally defined as either symptom management and/or tumor control, specified at the time of initial consultation.	100%	B
2. What tool should be used to estimate performance status in the setting of metastatic disease?	All patients being treated for non-spine bone metastases should have, at minimum, Karnofsky Performance Status (KPS) or ECOG, determined and documented at time of initial consultation.	100%	A
3. How are uncomplicated bone metastases defined, and what is the preferred treatment for symptomatic uncomplicated bone metastases?	A. Uncomplicated bone metastases can be defined as: painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression, and which have not had prior local therapy. B. Radiation is first-line treatment for symptomatic uncomplicated bone metastases.	88%	A
4. What clinical scenarios of non-spine bone metastases can be classified as "complex," and should be <u>considered</u> for review by a multidisciplinary team?	Clinical scenarios that can be classified as "complex" and therefore warrant review by a multidisciplinary team include, but are not limited to: Pathologic fracture or impending fracture Recurrence after initial local therapy to metastatic lesion Difficulty determining origin of a patient's pain (i.e. multiple lesions, defining mechanical vs. biological pain) Oligometastatic disease (defined as <5 metastatic lesions) in a patient with >6 months prognosis and stable disease after first-line systemic therapy	94%	C
5. When should a patient with non-spine bone metastases be referred to surgery for prophylactic surgical fixation/stabilization?	Referral to a surgeon should be considered if the patient's medical status and oncologic life expectancy are permissive of surgery and **any** of the following are present: 1. Lytic long bone or pelvic lesion with pain that is worsened with activity, 2. Any significant lesion in the femur that is either lytic or painful, 3. Progressive growth after radiation, or 4. Failure of palliation with radiation	88%	B
6. When should referral to interventional radiology for image-guided <u>stabilization</u> (such as cementoplasty) be considered for a patient with non-spine bone metastases?	Percutaneous *stabilization* (e.g. cementoplasty, cemented screw fixation) should be considered for patients who have been evaluated by orthopaedic surgery and are not surgical candidates if the following are met: 1. The patient has mechanical pain (pain that is worsened by weight-bearing, positional changes, or activity) 4 or more weeks after radiation. 2. Metastatic lesion is in the pelvis or the epiphysis/metaphysis of a long bone with intact subchondral bone. There is insufficient evidence to guide the choice between various stabilization modalities or whether ablation and stabilization should be used concurrently.	88%	C
7. When should referral to interventional radiology for image-guided <u>ablation</u> be considered for a patient with non-spine bone metastases?	Percutaneous *ablation* (e.g. cryoablation, radiofrequency ablation, microwave ablation) should be considered for patients with symptomatic bone metastases if all of the following are met: 1. First-line radiation has not provided adequate pain relief (evaluated at least 4 weeks after treatment) and reirradiation is not preferred; 2. Metastatic lesion is in the pelvis, a long bone, the sternum, or the scapula; 3. Bone is not at risk for fracture; 4. Pain is non-mechanical; 5. Ablation target is at least 1 cm from functional neurologic elements, visceral organs, and joint surfaces. There is insufficient evidence to guide the choice between various ablation modalities or whether ablation and stabilization should be used concurrently.	81%	B
8. What radiation regimens are preferred for symptomatic uncomplicated non-spine bone metastases?	Most radiation treatments can and should be delivered in 5 or fewer fractions, regardless of technique (2D vs 3D vs SBRT).	100%	A
9. When should stereotactic radiation (SBRT/SABR) be considered for the treatment of non-spine bone metastases?	• For symptomatic patients, stereotactic radiation can be considered for those with high KPS (70+) and radioresistant histology, or in the setting of re-treatment when more conformal therapy is needed to avoid exceeding dose constraints. • For asymptomatic patients with oligometastatic disease, phase II randomized data for SABR is promising, although enrollment on a clinical trial is preferred until phase III data is available.	94%	B
10. What is the preferred approach to radiotherapy in the setting of stabilization surgery for non-spine bone metastases?	After stabilization surgery, coverage of the entire orthopaedic hardware within the radiation field is recommended to reduce local recurrence. There is insufficient evidence to recommend the use of pre-	81%	B

Table 1 (*continued*)

Question	Answer	% Agreement	Strength of Recommendation
	operative radiation therapy to a non-spine bone metastasis outside of a clinical trial.		
11.1 When should systemic therapies be held for patients undergoing radiation therapy for non-spine bone metastases?	Immunotherapy and hormone therapies (excluding hormone-based chemotherapy) are generally **considered safe and can be continued during radiation.** Potential exception may include radiation to organs that have had immunotherapy related complications.	94%	B
11.2 When should systemic therapies be held for patients undergoing radiation therapy for non-spine bone metastases?	For patients on VEGF and VEGFR inhibitors (i.e. bevacizumab), radiation fields that involve the bowel may increase the risk of bowel injury. However, due to the unclear duration of this risk before and after VEGF or VEGFR inhibitor dosing, as well as the long half-lives of antiangiogenic drugs, for select patients it may be reasonable to offer RT during or soon after administration of such agents. **Patients should be counselled on these risks prior to RT, and subsequent use of VEGF or VEGFR inhibitors after RT is discouraged.**	88%	C
11.3 When should systemic therapies be held for patients undergoing radiation therapy for non-spine bone metastases?	With regard to BRAF inhibitors (dabrafenib, vemurafenib, encorafenib) and MEK inhibitors, we defer to the 2016 ECOG guidelines, which recommend holding for at least 3 days before and after RT due to risk for skin toxicity.	100%	C
11.4 When should systemic therapies be held for patients undergoing radiation therapy for non-spine bone metastases?	When systemic agents have <u>known toxicities to organs that overlap</u> with the radiation field (e.g. doxorubicin with sternal metastases), consider holding systemic therapy for 2 half-lives.	94%	C
11.5 When should systemic therapies be held for patients undergoing radiation therapy for non-spine bone metastases?	For CDK inhibitors and other targeted therapies and cytotoxic agents, there is insufficient evidence to guide the decision on when to hold systemic therapy. Most palliative radiation trials defer to the treating physician's preference. **We hold these agents for 1-2 half-lives before radiation treatment, and for 24 hours after radiation.**	88%	C

therapy for oligometastases has a growing body of evidence, the definition and indications continue to evolve. The multidisciplinary setting allows for additional input regarding patient selection, timing with systemic therapy, and radiation dose.

Topic 5: Indications for surgical referral

Multiple retrospective studies have demonstrated that prophylactic stabilization of the femur may be associated with improved survival compared to surgery for a completed femur fracture [32,33]. Regardless, clinicians should aim to promptly refer for surgical evaluation those patients at imminent risk of pathologic long bone fracture, particularly in the femur, given known risk of morbidity and mortality caused by femur fracture [34].

Readily available morphology-based scoring tools for predicting pathologic long bone fracture have limited accuracy [35,36]. Nonetheless, a review by Siegel et al. points out that the presence of pain with weight bearing is likely the most important factor in determining risk for pathologic fracture [37]. Extent of cortical involvement and osteolytic lesions have also been shown to be associated with higher risk of pathologic fracture [38,39].

Topic 6: Considerations for percutaneous stabilization

Percutaneous stabilization techniques were introduced for patients with metastatic disease in the spine (e.g. vertebroplasty), but more recently have been used for individuals with non-spine bone metastases. Retrospective data have shown these procedures to provide short-term palliation for patients who have persistent pain despite RT and are not candidates for surgery [40,41]. One single-arm prospective study in which 50 patients with non-spine bone metastases were treated with cementoplasty after failure of conventional therapy reported durable pain relief with 9 months of follow-up, but two patients with lesions in the femoral diaphysis suffered femur fractures, [42] prompting our recommendation for consideration of cementoplasty only for lesions in the epiphysis or metaphysis of a long bone. Broader reviews of the data for percutaneous stabilization exist, though these are generally limited by heterogeneous groups of patients and difficulty separating the effects

of the percutaneous stabilization from other treatments [43–45]. Therefore, we reserve these techniques for patients in whom traditional treatments are contraindicated or ineffective.

Topic 7: Considerations for percutaneous ablation

As stated above, radiation therapy is an effective first-line treatment for alleviation of pain in patients with non-spine bone metastases. However up to 40% of patients will not achieve pain relief after first-line RT [29]. For these individuals, retreatment with radiation therapy is generally safe and provides pain relief in about half of cases [46,47]. However in some cases reirradiation may prove ineffective or challenging due to adjacent normal tissue dose constraints or a patient's inability to tolerate simulation and treatment. In these situations, percutaneous ablation provides an alternative.

Goetz et. al. conducted a single-arm prospective study in which patients who had failed standard therapy and been seen by a radiation oncologist were treated with radiofrequency ablation, and experienced clinically significant pain relief up to 24 weeks after the procedure [48]. Other studies of percutaneous ablation have been done, but have heterogeneous patient populations and often use ablation in combination with cementoplasty, making conclusions about the effectiveness of ablation difficult [40,43]. Patients who are at high risk of pathologic fracture are not good candidates for percutaneous ablation and should be referred to an orthopaedic surgeon.

Topic 8: Radiation treatment for symptomatic uncomplicated bone metastases

Multiple prospective randomized trials have demonstrated that single fraction regimens are as effective as multi-fraction regimens for symptom relief for bone metastases [49–53]. However, single fraction regimens are more likely to require retreatment, which has been shown to have limited use in routine practice [54]. A small randomized trial demonstrated equivalence between 5- and 10-fraction regimens in terms of pain relief and time to retreatment [55]. Meanwhile, trials have shown safety and efficacy of stereotactic treatments delivered in 1–5 fractions [56,57], and preliminary data suggests reductions in financial toxicity with shorter SBRT

regimens for metastases [58]. It is therefore important to minimize the burden of treatment visits for patients with metastatic disease, and we recommend treatment in no more than 5 fractions for those with symptomatic, uncomplicated non-spine bone lesions.

Topic 9: Considerations for stereotactic radiation

In the palliative setting, a phase II randomized controlled trial showed single fraction SBRT to be non-inferior to multi-fraction conventional RT, with higher rates of pain response in those receiving SBRT [57]. We favor using conventional RT for bone metastases in most cases, with SBRT reserved for patients at high risk for recurrence, in particular those with radioresistant tumors or prolonged expected survival [5].

Phase II data for the use of ablative radiation for patients with oligometastases are promising [59,60], with the strongest evidence in patients with lung cancer [59], however patient selection is likely important and therefore such treatments remain largely investigational and presentation to a multidisciplinary team (as noted above) or enrollment in a clinical trial is preferred.

Topic 10: Combining surgery and radiation

Multiple retrospective analyses have shown that rates of local recurrence are lower for patients who receive RT to the entire length of orthopaedic hardware after stabilization surgery [61,62]. Pre-operative radiation to non-spine bone metastases is an area warranting further research, with a prospective clinical trial underway.

Topic 11: Holding systemic therapy during radiation

Immunotherapy and hormone therapy agents are most likely safe to administer during radiation, although limitations in the data still exist. Phase I trials have shown that concurrent immunotherapy and RT is safe, and the effectiveness of this combination may be promising for certain patients [63,64]. Hormonal therapy is also safe when used concurrently with RT, as demonstrated by several large retrospective analyses in the primary breast cancer population which did not show meaningful safety concerns [65,66].

The safety of VEGF or VEGFR inhibiting drugs when used with RT is not well established. Multiple case reports and case series have shown a risk of gastrointestinal (GI) toxicity when abdominal sites are treated with radiation, either concurrently with VEGF/VEGFR inhibitors, or as much as 17 months prior to use of these agents [67–70]. Holding these drugs has an unclear effect on the risk of toxicity, and due to the long half-life of bevacizumab, may not be feasible. The risks and benefits of treatment should be discussed with each individual patient for whom VEGF inhibition and RT is being considered.

BRAF inhibiting agents carry a risk of skin reactions when used concurrently with RT, in addition to other less common toxicities. A literature review and consensus process conducted by the ECOG in 2016 recommended that BRAF inhibitors be held for at least 3 days before and after fractionated RT, and at least 1 day before and after stereotactic radiosurgery (SRS), which we support [71].

On the basis of expert opinion, we recommend holding chemotherapeutic agents when the toxicity of the agent overlaps with the site to be irradiated, such as holding doxorubicin when irradiating a sternal metastasis. We hold these agents for 2 half-lives before and after radiation.

CDK inhibitors have an unclear safety profile when used with radiation. The risk of neutropenia does not appear to be different than with CDK inhibitors alone [72], and a small retrospective study showed combination treatment to be safe [73]. Alternatively, other studies have raised concern for pulmonary, GI, and skin toxicities [74–77]. Due to the dosing schedule of palbociclib, RT can be delivered during the week when patients are not receiving the drug. For other CDK inhibitors, we recommend holding for 1–2 half-lives before RT and 24 hours after.

Most other chemotherapeutics and targeted agents have not been thoroughly studied in the setting of concurrent use with RT. We generally hold other chemotherapy and targeted agents for 1–2 half-lives before RT and 24 hours after.

Discussion

This study confirms that a consensus process among multidisciplinary oncologists in an academic-community partnership is feasible, and can address gaps in available national guidelines, even in the absence of level 1 evidence. This process resulted in an updated review of the evidence underpinning local treatment of non-spine bone metastases, including patient selection for surgical management, complex radiation and interventional radiologic approaches, appropriate radiation regimens and field designs, and safe approaches to continuing systemic therapy during radiation.

This initiative provides recommendations for clinicians to use in their practice treating non-spine bone metastases while facilitating opportunities to reduce variation in diverse practice settings which can benefit patients seeking care close to home. Most notably, our recommendation for treatment with 5 or fewer fractions is novel and clinically actionable. It builds upon prior publications advocating for high-value patient-centered short-course regimens [3,78] by integrating known barriers to uptake of single fraction [54] while allowing newer techniques such as SBRT. It has therefore been selected as the primary endpoint of a future prospective implementation trial.

Our consensus process also elucidated areas with a relative lack of prospective data. Specifically, uncertainty exists about the definition of the oligometastatic state and proper management for these patients. While some patients appear to benefit from metastasis-directed therapy, optimal patient selection remains unclear. Trials are underway, for example, to determine how many metastases can be effectively treated with local therapy [79], the role of RT for asymptomatic lesions in high-risk sites, and the role of pre-operative RT for patients requiring stabilization surgery. Other areas that require further study are pathologic fracture prediction models, and the optimal candidates for percutaneous interventions. Nonetheless, a framework for considering these emerging techniques is provided.

Our study does have several limitations. First, both topic questions and responses may be biased by the experts selected for the panel. However, we conducted a systematic literature review and included multi-disciplinary physicians from both academic and community-based practice to represent a range of perspectives with the intent of being generalizable. Second, our consensus process was conducted within the context of an existing academic-community partnership, and therefore certain recommendations may be difficult to implement in other settings. Nonetheless, these recommendations may still help oncologists determine when referral is potentially beneficial. Third, several of the questions that were identified for consensus lacked high-level evidence, given the rapidly changing nature of the field. We chose to provide recommendations based upon the available data and expert opinion on such topics, in response to a survey of oncologists showing that in the absence of high-level evidence, clinicians prefer guidelines based upon expert opinion to no guidelines [80].

Our results are relevant to practicing oncologists treating non-spine bone metastases, as well as clinical researchers, highlighting areas where further study is needed. As treatment for metastatic cancer continues to evolve, it is crucial that efforts are made to ensure the benefits of treatment are provided to all patients, regardless of practice setting and geographic location.

Declaration of Competing Interest

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

Data Availability

Research data for this study are stored in an institutional database and are available upon request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.04.009.

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