

Editorial

ASTRO Editorial: The Multidisciplinary Management of Metastatic Disease of the Femur: Toward Optimizing Outcomes

Yolanda D. Tseng, MD,^{a,*} Kilian E. Salerno, MD,^b and Tracy A. Balboni, MD, MPH,^c on behalf of the American Society for Radiation Oncology's Guideline Subcommittee

^aUniversity of Washington, Department of Radiation Oncology, Seattle, Washington; ^bNational Cancer Institute, Radiation Oncology Branch, Bethesda, Maryland; and ^cDana-Farber/Brigham and Women's Cancer Center, Department of Radiation Oncology, Boston, Massachusetts

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Distant spread of carcinoma to the bone is a common site of metastatic disease, with the spine, pelvis, and ribs most frequently involved.^{1,2} In contrast, femoral involvement is less commonly seen, occurring in 5% to 25% of patients with advanced cancer.^{1,2} Nonetheless, the femur is the most common long bone affected by carcinoma and multiple myeloma, with the proximal femur as a frequent site of fracture in patients with metastatic disease.^{3,4} Compared with other sites of bone metastases, femoral metastases are associated with the potential for increased morbidity, with impact on quality of life through pain, impaired function and mobility, and risk of pathologic fracture. Local treatment options include radiation therapy (RT), surgery, surgery followed by RT, or observation. Given the multiple treatment options and limited randomized data to inform evidence-based decision making, the optimal management of femoral metastases is well suited for a multidisciplinary collaboration

between each patient and their radiation oncologist, medical oncologist, and orthopedic surgeon.

What questions should these multidisciplinary discussions answer, and what factors influence the decision-making and treatment selection? The first factor is the identification of patients at a high risk for future pathologic femoral bone fracture. Assuming no fracture is currently present, the second corollary is the prevention and identification of the optimal management for patients with different risks of fracture. Patients may be categorized by the presence or absence of symptoms and whether the future risk of fracture is low or high. Also, which patients require prophylactic surgical stabilization followed by RT, RT alone, or no local therapy at all? Unfortunately, there are limited data on defining risk of pathologic fracture and optimal treatment for femoral metastases.

To this end, a multidisciplinary collaboration among work group members from the Musculoskeletal Tumor Society, American Society of Clinical Oncology, and American Society for Radiation Oncology recently developed a clinical practice guideline with specific focus on the management of metastatic carcinoma and myeloma of the femur (<http://msts.org/index.php/education/evidence-based-medicine>). Prior guidelines focused more broadly on the management of bone metastases or by histology. This recent guideline is novel given its sole

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* Corresponding author: Yolanda D. Tseng, MD; E-mail: ydt2@uw.edu

focus on femoral metastases and is the first guideline to incorporate orthopedic surgeons in collaboration with radiation and medical oncologists. Some guidelines synthesize an abundance of available data into recommendations to guide management, but others (as is the case with this guideline) demonstrate the paucity of available evidence to address common yet complex clinical scenarios and thus rely more heavily on multidisciplinary, expert consensus. This guideline is valuable in helping to identify current gaps in the literature, filling those gaps with multidisciplinary expert consensus, and highlighting directions for future research.

Fifteen patient, intervention, comparison, and outcome (PICO) questions were initially proposed for this guideline. A comprehensive systematic database search of pertinent literature was conducted through July 2019. There was sufficient information to meet the strict inclusion and quality standards to make evidence-based recommendations for only 4 of these questions, which was due in part to the guideline's narrow scope of femoral metastases and explains why much of the palliative radiation bone metastases literature familiar to radiation oncologists were not included in the evaluated evidence. Studies had to include a minimum of 10 patients with metastatic carcinoma or multiple myeloma, focus on the femur, and be comparative in nature. Only 23 articles met these strict inclusion criteria. Thirteen recommendation statements were made, and the strength of each was graded based on the level of available evidence, risk/benefit ratio of treatment, accessibility, and magnitude of treatment effect, and voted on by the work group members.

Among the evidence-based recommendations, only one had the highest strength of recommendation (strong): Decreasing the frequency of bone-modifying agents from the standard 4-week interval to every 12 weeks. Two RT-related recommendations garnered the next highest strength of recommendation (moderate). These recommendations highlight the role of RT in the management of femoral disease.

Radiation should be considered to reduce the risk of femur fractures in patients deemed to be at an increased risk based on the combination of imaging findings and lesion-related pain. The use of multifraction dose/fractionation schedule over a single fraction should be considered to reduce the risk of femur fracture. The recommendations were based on limited evidence (observational data⁵ and a single randomized trial⁶) and would have been graded as limited given the few supporting studies. However, given the high morbidity of a femoral fracture, including increased surgical difficulty, and the low toxicity profile of RT to the femur, the recommendation was upgraded to moderate. Additionally, adjuvant RT was recommended, although with the lowest strength

(consensus), after prophylactic femur stabilization or resection and reconstruction.

The guideline acknowledges the absence of reliable evidence to identify predictors for femoral fracture. This is one of the critical questions to answer in multidisciplinary decision-making; therefore, the work group provided a consensus recommendation that the 2 important predictors of pathologic fracture risk are imaging findings and lesion-related pain. This still leaves much to interpret by the radiation and medical oncologists involved in the care to determine which patients should be referred for orthopedic evaluation. Approximately 10% of patients treated with RT alone to the femur suffer a subsequent pathologic fracture.⁷ The guideline does not elaborate further on specific radiographic predictors, but commonly used criteria include the Mirel's scoring system, which is based on 4 metastasis characteristics: Pain, location, lesion morphology (ie, sclerotic versus lytic), and extent of cortical involvement.⁸ Also frequently used are the criteria found to predict pathologic fracture in a subanalysis of femur metastases treated within the Dutch bone metastasis randomized controlled trial (lesion size >3 cm and >50% cortical involvement).⁶

Unfortunately, very few radiation oncology studies were identified to inform recommendations. Furthermore, not all relevant RT questions could be addressed within the scope of this guideline. Given the known effect of RT on the palliation of bone pain, there is less uncertainty on the role of RT in the management of patients with symptomatic disease. However, the indication for RT as prophylaxis in patients with asymptomatic femoral metastasis is less clearly defined.

How should we as radiation oncologists implement this guideline in practice? The guideline affirms the role of imaging findings and pain in assessing fracture risk and hence who should be considered for orthopedic evaluation, the benefit of RT to reduce the risk of femoral fractures, and the importance of considering multifraction RT to ameliorate the risk of future fractures. The guideline also highlights knowledge gaps and opportunities for future research, including whether we should approach multiple myeloma and metastatic carcinoma management of femur lesions differently (eg, for dose/fractionation schedule), predictors for local recurrence after irradiating femur lesions, and whether asymptomatic patients require RT or other local therapies. Other unanswered questions include the cost effectiveness of arthroplasty compared with other surgical techniques and the optimal management of atypical femur fractures. Lastly, given that our available evidence base is limited to answer clinical questions, priority should be given to a multidisciplinary team-based approach for evaluation and discussion. Patient prognosis, performance status, preferences, and

goals of care should be incorporated into shared clinical decision-making.

In summary, the optimal management of metastatic carcinoma to the bone and multiple myeloma with femoral involvement is complex, involves a wide spectrum of presentations, and has many local treatment options spanning observation to RT, surgery, or both. Given the risk for morbidity, especially pathologic fractures, and the impact on quality of life and function, such treatment decisions are best managed with a multidisciplinary collaboration between radiation oncologists, medical oncologists, and orthopedic surgeons in conjunction with each patient.

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