A phase II trial on radiotherapy for high-risk asymptomatic bone metastases—creating more questions than answers?

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It is well known that bone metastases can significantly reduce quality of life due to related symptoms and possible life-changing complications. Common presentations include pain and neurologic deficits. The most serious complications of bone metastases are skeletal-related events (SREs), defined as pathologic fracture, spinal cord compression, or other events requiring an urgent surgical or radiation intervention. Growing access to modern diagnostic tools and the frequency of surveillance imaging performed in patients with diagnoses of cancer allow early detection of asymptomatic bone metastases that could be considered for prophylactic intervention aimed at trying

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to avoid the development of SRE. Improved systemic treatment, including the increasing use of immunotherapies and targeted therapies, are also prolonging survival, which may lead to a higher prevalence of both bone metastasis and SRE over time.

Although radiotherapy (RT) has a well-established role in the treatment of painful bone metastases, data are limited in the asymptomatic setting. Specifically, the European Society for Therapeutic Radiology and Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (ACROP) guidelines for external beam RT of patients with uncomplicated bone metastases recommend against the use of palliative RT for asymptomatic bone metastasis because of lack of clear evidence. Uncomplicated bone metastasis was defined as painful bone metastasis without impending or existing fracture and without spinal cord or cauda equine compression (1). The guideline on complicated bone metastases, however, does note that a lesion at risk for fracture should be considered for treatment based on multidisciplinary discussion (2).

Against this background, Gillespie *et al.* conducted a multi-center randomized controlled phase II trial that compared RT to sites of asymptomatic high-risk bone metastasis *vs.* standard of care (SOC) alone in patients with widely metastatic solid malignancies (3). This trial was published at a time when there is increased awareness of early treatment for bone metastases to prevent complications. For instance, preventive stabilization surgery has recently been suggested for vertebral metastases with high Spinal Instability Neoplastic Score (SINS) (4).

In their trial, Gillespie *et al.* defined high-risk bone metastases as bone metastases with at least one of the following adverse features: (I) greater than 2 cm; (II) involving the hip, shoulder, or sacroiliac joint; (III) occupying one-third to two-thirds of the cortical thickness of a long bone; or (IV) located at a junctional spine or with posterior element involvement (5). The primary endpoint was the occurrence of SRE, also including the need for RT for pain, whereas the secondary endpoints included hospitalization for SRE and overall survival (OS). At 1 year, there was a significant reduction of SRE in the RT arm compared with the SOC arm (1.6% *vs.* 29%, P<0.001). Remarkably, OS was also significantly longer in the RT arm (hazard ratio, 0.49; P=0.018).

While the results of the trial are impressive, several things need to be considered when interpreting the findings of this study. Gillespie *et al.* did not specify in their trial protocol the imaging modalities that were used to diagnose the high-risk bone metastases (6). Imaging modalities vary in their sensitivity to diagnose bone metastases. For instance, magnetic resonance imaging (MRI) is more sensitive to bone marrow infiltration and can detect small lesions before they result in bone destruction that could be detected by computer tomography (CT) (7). Therefore, a junctional spine metastasis that is detectable only in MRI is likely at a lower risk of fracture compared with a lesion that has bone destruction visible in CT. Moreover, the trial by Gillespie did not use any validated tools to quantify the fracture risk, such as the Mirels' score for metastases in long bones (8). The use of such fracture assessment tools in clinical trials, as well as reporting on the type of imaging modality used to detect the bone metastases, may provide a more accurate and reproducible assessment of the fracture risk at baseline. Clinicians can then use the same tools to evaluate whether the asymptomatic bone metastases of patients that they are seeing in their clinic would have the same fracture risk or potentially derive the same magnitude of benefit compared with the patients in the clinical trial. Equally, the SINS is important in assessing the vertebral metastases.

The study by Gillespie *et al.* also raises the question of whether imaging tests that are highly sensitive for bone metastases, such as positron emission tomography (PET)-CT or MRI, should be performed to screen for asymptomatic high-risk bone metastases to allow early treatment. This was the research question in the UK PROMPTS trial, which evaluated the potential benefit of screening spinal MRI and pre-emptive RT for radiological spinal cord compression in patients with castration-resistant prostate cancer (9). They found that the incidence of clinical spinal cord compression at 1 year was not improved. Based on the result, the investigators suggested that the routine use of screening MRI to prevent clinical cord compression was not warranted. Additionally, having regular cross-sectional studies to look for asymptomatic bone metastases might divert resources away from other patients in some healthcare systems. This can be particularly problematic in low- and middle-income countries. Even in high-income countries, resources spent on such efforts can delay the upfront staging in other cancer patients eligible for curative treatments. Given the above, studies are needed to clarify the type and frequency of imaging modalities that are needed to detect high-risk bone metastases.

Around 50% of the patients in the study by Gillespie *et al.* were on bone modifying agents (BMAs), which may also affect the primary outcome of SRE as a potential

confounder. A recent study showed that the use of bisphosphate during or after RT for lytic spinal metastases was associated with a greater increase in bone mineral density (10). Lower bone mineral density has been suggested to be predictive of vertebral compressive fracture after RT for spine metastases (11). It will be interesting to assess whether patients on and not on BMA could derive the same magnitude of benefit from prophylactic RT. Furthermore, denosumab has been shown to be more effective than zoledronic acid in preventing SRE (12). A future phase III clinical trial may perform subgroup analysis to look at the interaction between the efficacy of prophylactic RT and the use or the type of BMA.

The trial by Gillespie *et al.* also allowed a wide range of dose-fractionation schedules, including the delivery of 8 Gy single fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions by conventional external beam RT (cEBRT), as well as 27 Gy in 3 fractions by stereotactic body RT (SBRT). The optimal dose-fractionation schedule remains to be defined. There is overwhelming evidence to show that compared with multi-fraction RT, 8 Gy single fraction provides equivalent pain response in uncomplicated bone metastasis and similar motor response and bladder dysfunction in spinal cord compression in patients with poor performance and limited estimated survival (13,14). In painful spine metastasis, SBRT has been shown to provide superior local control compared with cEBRT, with dose escalation beyond 24 Gy in 2 fractions providing further benefit (15-17). In painful non-spine metastasis, SBRT can also achieve a higher local control compared with cEBRT (18). SBRT may be especially suitable for patients with good prognosis and live long enough to see this potential long-term benefit in local control. But these data may not be applicable to asymptomatic high-risk or complicated bone metastases. SBRT is contraindicated in certain situations for fear of SBRT-induced iatrogenic fractures both in spine and non-spine bone metastases. While a multi-fraction regimen may potentially result in better local control and remineralization in lytic bone metastasis, the preferred dose-fractionation schedule in asymptomatic high-risk or complicated bone metastasis has not yet been addressed by any randomized controlled trial (19,20). A future dose-finding trial investigating the role of RT in asymptomatic high-risk bone metastasis should identify the most efficacious dose-fractionation schedule prior to launching a definitive phase III randomized study.

Additionally, the apparent benefit in the OS in the prophylactic RT arm needs to be closely examined. While the study by Gillespie *et al.* showed that there were seven deaths and four hospitalizations prevented by RT compared with the SOC group by 1 year, it is unclear as to why the number of deaths prevented exceeds the number of hospitalizations prevented. Life-threatening SRE, such as debilitating spinal cord compression or long bone fracture that cause significant functional decline, often lead to hospitalization before causing death. If the improvement in OS is mediated by a reduction of SRE, we may expect a corresponding or even greater decrease in hospitalizations in the RT arm. This raises questions about other possible causes of the improvement in OS seen in that study. Baseline characteristics, such as the Karnofsky Performance Status (KPS), were not balanced, with 62% of the patients in the prophylactic RT arm having KPS or 90 or above *vs.* 46% in the observation arm. The extent of visceral metastases, the use of effective systematic therapy, and other co-morbid conditions were not reported nor attempted to be balanced in both arms, and they are critical in determining the OS of patients with advanced malignancies. These factors might explain, in part, the better survival in the prophylactic RT arm.

Use of palliative RT for bone pain was included as an SRE in the study by Gillespie *et al.* Since it is at the treating clinician's sole discretion whether to give RT for the bone metastasis, the rate of SRE could be biased as a result. To address this concern, the authors did run an unplanned analysis limited to SRE excluding palliative RT for bone pain, and the result remained to be significant. In addition, Gillespie *et al.* reported that the time-to-SRE at the bone metastasis level varied significantly on the basis of the enrolled lesion's definition of high risk, with descriptively more events in junctional spine and bulky sites of disease. A dedicated subset analysis might be warranted in future trials to evaluate the magnitude of benefit of RT across the different indications.

Another important issue is the other side effects induced by RT in these patients with asymptomatic bone metastases. RT has been shown to cause pain flare and other symptoms (21). Acute pain flare has been reported to have an incidence as high as 68% in SBRT and around 40% in patients treated with cEBRT despite the use of dexamethasone (22,23). The pain typically resolves within a median of 3 days (24). These need to be balanced for the potential benefits and side effects in the setting of metastatic cancer, though there are little data regarding the incidence of pain flare after RT for asymptomatic bone metastases. Do no harm is still an important aim to follow unless benefits outweigh toxicities substantially.

Furthermore, patient preference is important to guide the interventions. In patients with rapidly progressive visceral metastases dependent on systematic therapy, delaying or interrupting such an important treatment in order to deliver radiation treatment of asymptomatic bone metastases may have potentially serious consequences and thus require multidisciplinary discussion and co-ordination. We have abundant trials in radiation treatment on patients with symptomatic bone metastases (25). These trials have most typically aimed to provide symptomatic relief without the intention of prolonging survival. There have been trials of radiation *vs.* best supportive care with the intent of avoiding futile radiation treatment, especially in the setting of end-of-life care (26). They are obviously different in patients with asymptomatic bone metastases, but the principle is still the same: providing benefits with minimal toxicities.

Lastly, this study was a relatively small phase 2 trial with limited power, with 78 patients enrolled and 73 evaluable for the primary endpoint. Further, the authors had inflated the sample size by allowing multiple sites per patient (122 treated lesions in total). Although it is commonly employed in the literature, this may bias the results towards patients with larger numbers of treated sites, as their outcomes may potentially be unrepresentative of the overall eligible population.

In view of the issues discussed above, a future phase III trial in this patient population is warranted and should provide details on the imaging modality used to diagnose the bone metastases, perform subgroup analyses for SBRT *vs.* cEBRT, the use of BMA and the indication of RT, and describe the causes of death to aid interpretation of the effect of prophylactic RT on OS. The use of standardized tools to assess the fracture risk and patient stratification according to factors that may affect the OS, such as the presence of visceral metastases, could be beneficial as well. Other ongoing trials, such as NCT05534321, may provide further data on prophylactic RT of minimally symptomatic bone metastasis (27). In addition, it is important to collaborate with other specialties such as medical oncologists, palliative care physicians, and orthopedic surgeons, to improve early and prompt referral to the RT departments to increase generalizability of the trial findings. With the advances in medical imaging and RT techniques, we now have the option of detecting and treating asymptomatic lesions with acceptably low toxicity. Therefore, it is critical to closely examine the evidence before offering any treatment or changing the SOC for these patients, because ultimately our decision should rest on what can benefit our patients rather than what we are capable of delivering.

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Footnote

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