Bone scan use in the management of metastatic castration-resistant prostate cancer: Survey of practice patterns among Canadian radiation oncologists, medical oncologists, and urologists

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Introduction

The use of skeletal scintigraphy with technetium-99 methylene diphosphonate (hereafter referred to as a bone scan) for evaluating response to systemic treatment in men with metastatic castration-resistant prostate cancer (mCRPC) is an evolving paradigm in this era of advancing therapies and imaging techniques. Indeed, the interpretation of bone scans can be challenging, and there is a growing expectation that advanced imaging techniques, such as prostate-specific membrane antigen positron emission tomography/computer tomography (PSMA PET/CT) may play a complementary role.[1] The Prostate Cancer Working Group (PCWG) has outlined specific criteria to define disease progression with respect to bone scans performed as part of clinical trials.[2] However, there is no high-level evidence for the scheduling and interpretation of bone scans during routine therapeutic interventions for mCRPC. Thus, patterns of bone scan use are variable and practice-dependent outside of clinical trials.

Methods

In this survey, approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Toronto, Canada), we sought to understand practice patterns of bone scan use in the management of mCRPC among Canadian radiation oncologists, medical oncologists, and urologists, as well as their experience with new imaging techniques. A letter of invitation including a description of study objectives and an embedded web link to complete the survey was distributed through the internal emailing lists of the Genitourinary Medical Oncologists of Canada (GUMOC), Genitourinary Radiation Oncologists of Canada (GUROC), Canadian Urological Oncology Group (CUOG), and Canadian Association of Radiation Oncology (CARO). The survey was administered through SurveyMonkey® (Palo Alto, CA, U.S.) for anonymous submission. A gift certificate was offered to each respondent at the completion of the survey. The first set of invitations was sent on March 27, 2018 and the survey remained active for seven months. Responses were analyzed using descriptive statistics in the form of frequencies and percentages. Responses to rank order questions were analyzed comparatively using stacked bar charts.

Results

We had a total of 91 participants in our survey consisting of 45.0% radiation oncologists (41/91), 37.4% medical oncologists (34/91), and 17.6% urologists (16/91). Most were from Ontario (53.3%) and British Columbia (24.4%), working in an academic setting (75.8%), and treating either 10–25 patients (40.4% of respondents), 25–50 patients (36.0%), or >50 mCRPC patients (23.6%) in a given year._

While 94.3% of respondents indicated they would order a baseline bone scan prior to initiating a new line of systemic therapy, about half (51.7%) replied they would forgo scheduling bone scans in asymptomatic men on treatment (Table 1). One in five indicated they would order bone scans in asymptomatic men if the prostate-specific antigen (PSA) doubling time was alarming. The percentages of physicians who routinely schedule a bone scan every 3–4 months, six months, or 12 months in men on therapy were 2.2%, 13.5%, and 12.4%, respectively, largely independent of the treatment used. Almost half of respondents (47.7%) confirmed signs of progression on a bone scan with additional imaging, with one-third (32.6%) ordering a followup bone scan to exclude a potential flare phenomenon.

Table 1. Use of bone scans in the management of metastatic castration-resistant prostate cancer

Is a baseline bone scan performed when initiating new treatments? (N=87)	n (%)
No	5 (5.7%)
Yes	82 (94.3%)
How often are scheduled bone scans performed on asymptomatic patients receiving treatment (N=89)	
No scheduled bone scan	46 (51.7%)
Every 3–4 months	2 (2.2%)
Every 6 months	12 (13.5%)
Every 12 months	11 (12.4%)
Frequently depending on PSA kinetics	18 (20.2%)
Does the type of therapy affect the frequency of obtaining a bone scan? (N=82)	
No	77 (93.9%)
Increase frequency if treatment with radium 223	5 (6.1%)
Is a bone scan progression confirmed with additional imaging? (N=88)	
No	46 (52.3%)
CT only	26 (29.5%)
CT and/or MRI	11 (12.5%)
CT and/or X-ray	3 (3.4%)
MRI only	2 (2.3%)
Is a suspected progression in bone scan (within 12 weeks of starting a new treatment) confirmed with a repeat bone scan? (N=89)	
No	60 (67.4%)
If yes, when?	
2–3 months	16 (18.0%)
4–6 months	4 (4.5%)
Depends on symptoms PSADT, clinical trial requirement	9 (10.1%)

CT: computed tomography; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; PSADT: PSA doubling time.

Symptoms (72.7%) and rising PSA (60.7%) were the two most frequently cited triggers for ordering a non-scheduled bone scan.

When asked to rank several measures of treatment response in order of clinical significance, symptomatic progression and skeletal-related events were ranked most commonly in the top two two (Fig. 1). Most respondents (80.4%) ranked bone scan progression as less important (i.e.. third to fifth position for clinical significance).

To determine bone scan-related progression, 81% of participants wrote they rely on the wording of the bone scan report, with 64% analyzing the bone scans themselves, 24% using PCWG3 criteria, and 9% correlating bone scan findings with sites of symptomatic disease. Only 1% use the bone scan index.[3]

Routine use of advanced imaging, such as PSMA, 18F-NaF, and 18F-fluciclovine PET/CT, was low at the time of the survey: 2.2% (2/89), 1.1% (1/89), and 0% (0/89) of participants, respectively.

Discussion

In men with mCRPC to bones, accurate, easily accessible, and validated biomarkers of response remain enigmatic, and clinical guidelines for assessing response to systemic therapy are relatively vague and heterogenous.[4-7] Hence, it is perhaps not astonishing that our survey shows significant variability in how bone metastases are monitored and how progression is defined.

While bone scan reports often subjectively indicate if there is a change in the burden of disease, they may fail to precisely quantitate the disease burden, thus rendering the report valuable primarily for identifying "progression," "stable disease/no progression," and "response." To distinguish between flare and progression on treatment, the PCWG3 has defined the latter as, "At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)."[2]

Currently, mCRPC progression is typically defined by clinical symptoms, PSA changes, and imaging (both in bone and soft tissue), with high clinical significance attributed to symptoms.[5] Likewise, our respondents viewed progression on bone scans in asymptomatic patients as a less relevant indicator of progression when making treatment decisions. On the other hand, the analysis of two large phase 3 trials suggests that radiographic progression-free survival in men with mCRPC (using PCWG3 criteria) is a robust surrogate for overall survival.[8,9]

Historically, the mainstay of treatment for men with mCRPC has been systemic therapy, and the question of progression and when to switch treatment has been a binary choice. Presumably, changes in PSA levels and symptomatic progression would suffice then. However, recent advances suggest that there might be an important opportunity to treat men with oligometastatic prostate cancer with metastasis-directed therapy (MDT).[10] This approach is supported by encouraging results from the SABR-COMET (all cancers),[11] STOMP (castration-sensitive oligorecurrent prostate cancer),[12] and ORIOLE (castration-sensitive oligometastatic prostate cancer)[13] phase 2 clinical trials. Furthermore, there are several ongoing phase 3 clinical trials seeking to definitively demonstrate the benefit of MTD in prostate cancer, including two Canadian studies: PLATON/PR.20 (NCT03784755) and PCS IX (NCT02685397). The results of these trials may further guide how closely we want to follow mCRPC to bone.

The results of our study should be interpreted in light of some limitations, including the relatively small sample size, ineffectiveness in capturing nuanced responses through close-ended questions, and under-representation of community practitioners treating mCRPC.

Conclusions

Consistent with the lack of consensus among clinical guidelines, our findings provide evidence of marked variation in practice around scheduling bone scans for assessing treat-

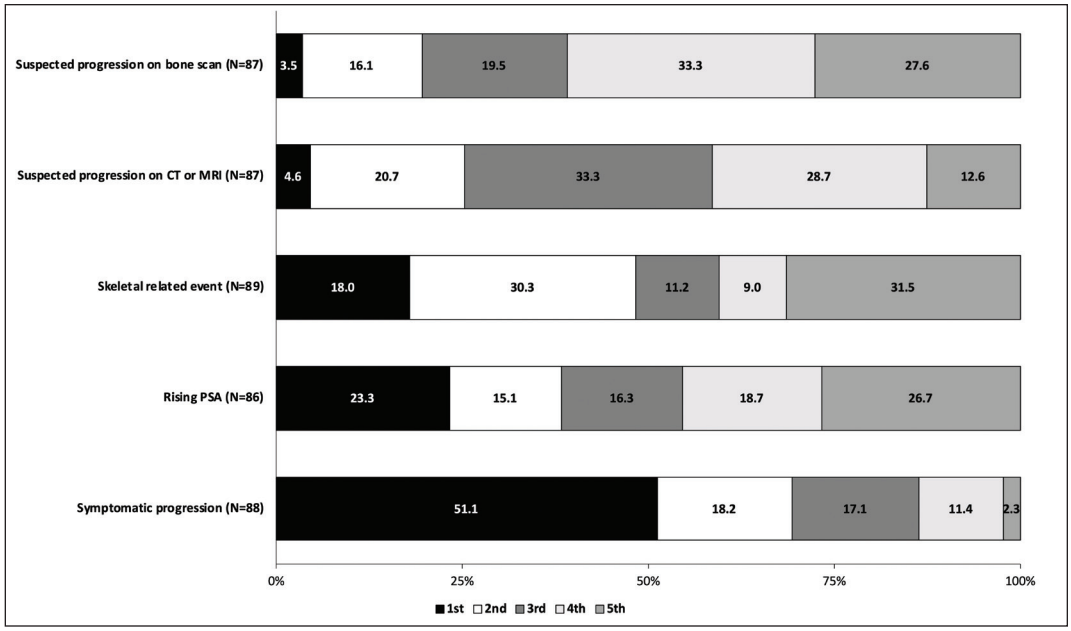

Fig. 1. Frequency of clinical measures of treatment response used for therapeutic guidance (ranked from 1st to 5th in order of importance; percentage of respondents). CT: computed tomography; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

ment response and disease progression in men with mCRPC. Physicians rely predominantly on change in symptoms for therapeutic guidance. Encouraging results from recent trials treating oligometastatic disease with MDT and ongoing Canadian trials exploring the benefit of MDT in men with prostate cancer may result in a fundamental change in the treatment paradigm of mCRPC. Arguably, therapy of mCRPC may shift from a systemic approach to one where systemic agents and MDT are combined for improved patient survival. Hence, accurately identifying the burden of disease in men with mCRPC, even in asymptomatic patients, could emerge as a crucial step in management.

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