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# Response Criteria:
## Prostate Cancer Working Group 3

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# Objectives

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- Quiz
- Changes in PCWG3 compared to PCWG2
- Role of imaging
- Review reporting guidelines for
  - baseline assessment
  - progression
- Quiz answers

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# Quiz question #1

PCWG3 is a clinical trial guideline for which patient population?

A. Patients with initial diagnosis of prostate cancer
B. Patients with biochemical recurrence of prostate cancer
C. Patients with castration-resistant prostate cancer

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# Quiz question #2

For baseline and progression assessment of CRPC, which of the following statement is true about PCWG3?

A. Lymph nodes >2 cm are measurable
B. Visceral metastasis are either present or absent
C. Tc99m-MDP is used as standard bone scan

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# Quiz question #3

For imaging interval, which of the following statement is true about PCWG3?

A. Image q12 wks x 2 years, then q24 wks
B. Image q8 wks x 2 years, then q12 wks
C. Image q4 wks x 2 years, then q8 wks

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# Quiz question #4

How is new bone metastasis defined compared to baseline?

A. New at least one focal intense uptake on bone scan
B. New at least two focal intense uptake on bone scan
C. Two new uptake over two scans for total of four new sites

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# Prostate Cancer Working Group 3 (PCWG3)

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- Castration-resistant prostate cancer (CRPC)
  - Defined as progression despite androgen depletion therapy
  - Present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.
- PCWG provides a guideline for clinical trial for pts with CRPC
- Started in 2008 when taxels only Rx available; emerging drugs being tested for CRPC led to PCWG2 → 3

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Can Urol Assoc J. 2010 Dec; 4(6): 380–384.

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# Prostate Cancer Working Group 3 (PCWG3)

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- PCWG3 - how it's different from PCWG2
  - Distinguish adenoCA from non-adenoCA
  - Considers sequence and number of prior treatments
  - Encourage disease subtypes
  - Defines endpoints for transition non-metastatic→ metastatic

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# PCWG3 Imaging Measures

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Measuring outcomes and reporting: imaging and clinical measures

1. Reconsiders the mixed response designation, which may be a manifestation of disease heterogeneity
2. Advises recording whether disease progression represents growth of pre-existing lesions, development of new lesions, or both, and separately recording whether progression is occurring in a single organ or disease site *v* multiple sites
3. Suggests that the first post-treatment bone scan be used as the baseline scan with which all future bone scans are compared (Fig 2); also emphasizes the notion of response in bone, caused by the advent of novel bone-targeting agents
4. Advises recording the location of nodal disease (pelvic *v* extrapelvic) and visceral disease (lung/liver/adrenal/CNS) separately, because these sites have separate prognostic implications
5. Also advises monitoring up to five individual lesions per site of spread (eg, nodes, lung, liver as separate sites) to address disease heterogeneity
6. Proposes new criteria to define the first occurrence of metastatic disease in men with nmCRPC at enrollment
7. Highlights and defines the bone-related outcomes, SREs and SSEs, but suggests focusing on SSEs, which represent a more direct clinical benefit to patients
8. Introduces the concept of treatment beyond progression where clinical benefit by one or more disease manifestations is being observed, thus defining an objective of NLCB

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Abbreviations: CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; NCI, National Cancer Institute; NLCB, no longer clinically benefiting; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; SRE, skeletal-related event; SSE, symptomatic skeletal event.

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# Baseline assessment: PCWG2 vs. PCWG3

**Table 2.** Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

| Assessment | PCWG2 (2008) | PCWG3 (2015) |
|---|---|---|
| Imaging | | |
| Prostate/ prostate bed | Endorectal MRI | Retained, cross-sectional imaging of prostate region if applicable |
| Nodal | CT: Only nodes ≥ 2 cm were assessed for change in size | CT or MRI:<br>Nodes ≥ 1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic<br>Record pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to five nodes in total<br>Record new lesions *v* growth of pre-existing lesions, and sites of new lesions |

Abbreviations: ALK, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CT, computed tomography; CTCs, circulating tumor cells; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; $^{99m}$Tc MDP, $^{99m}$Tc methylene diphosphonate.

*Ultrasensitive testosterone measures may be indicated where appropriate on the basis of drug under study and context.

- Baseline: PCWG3 adopts RECIST 1.1 guidelines. Lymph nodes short axis ≥ 1.5 cm are measurable. 1.0- <1.5 cm as pathologic and <1.0 cm non-pathologic
- Also specifies if LN are pelvic only or extrapelvic because of differences in prognosis

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# Baseline assessment: PCWG2 vs. PCWG3

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**Table 2.** Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

| Assessment | PCWG2 (2008) | PCWG3 (2015) |
|---|---|---|
| Visceral | CT: reported as visceral per RECIST | CT or MRI:<br>Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to five lesions per site<br>Lesions ≥ 1.0 cm in the longest dimension are considered measurable<br>Record new lesions *v* growth of pre-existing lesions, and sites of new lesions |
| Bone | $^{99m}$Tc MDP | Record new lesions and sites of new lesions |

Abbreviations: ALK, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CT, computed tomography; CTCs, circulating tumor cells; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; $^{99m}$Tc MDP, $^{99m}$Tc methylene diphosphonate.

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- Baseline: PCWG3 specifies the sites of visceral disease (lung, liver, adrenal, CNS) separately

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# Progression assessment: PCWG2 vs. PCWG3



**Table 3.** Criteria for Progression at Trial Entry by Disease Manifestation

| Variable | PCWG2 (2008) | PCWG3 (2015) |
|---|---|---|
| Imaging | | |
| Nodes | Nodal progression sufficient for trial entry independent of PSA | Retained |
| | Measurable lesions not required for entry | Retained |
| | Use RECIST to record nodal lesions as target or nontarget | Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to five nodal lesions total recorded |
| | Only lymph nodes ≥ 2 cm in diameter (long axis) were actionable as progressive disease | Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed |
| | | If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable |
| | | For existing pathologic adenopathy, progression is defined per RECIST 1.1 |
| | Record presence of nodal and/or visceral disease separately | Retained with modification |
| | | Nodal sites: |
| | | Locoregional: pelvic only |
| | | Extrapelvic: retroperitoneal, mediastinal, thoracic, or other |

- Lymph nodes: PCWG3 endorses RECIST 1.1 guidelines
- For nodal metastasis, clarify if local regional (pelvic only) or extrapelvic (RP, mediastinal, etc) because this has prognostic implications.

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# Progression assessment: PCWG2 vs. PCWG3



**Table 3.** Criteria for Progression at Trial Entry by Disease Manifestation

| Variable | PCWG2 (2008) | PCWG3 (2015) |
|---|---|---|
| Viscera | Visceral progression sufficient for trial entry independent of PSA | Retained but recorded separately by site of spread (lung, liver, adrenal, CNS); up to five lesions per site of spread |
| | Measurable lesions not required for entry | Retained |
| | Use RECIST to record visceral lesions as target or nontarget | Retained |
| | Record presence of nodal and/or visceral disease separately | Retained with modification<br>Visceral sites: lung, liver, adrenal, CNS |
| Prostate/prostate bed (primary site) | Record prior treatment of primary tumor | Retained |
| | Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease | Retained |
| Bone | Two new lesions | Retained |
| | Confirm ambiguous results by other imaging modalities (eg, CT or MRI) | Retained, but only positivity on the bone scan defines metastatic disease to bone |
| Other sites of disease | Patients with treated epidural lesions and no other epidural progression are eligible | Retained |

- Progression in viscera, prostatic bed, bone and other sites are similar to PCWG2; in addition, PCWG3 clarifies sites of visceral metastasis

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# Imaging interval

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**Table 4.** Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

| Measure* | PCWG2 Frequency (2008) | PCWG3 Frequency (2015)† |
|---|---|---|
| Imaging | | |
| Bone scans | Every 12 weeks | Every 8 to 9 weeks for first 24 weeks, then every 12 weeks† |
| CT/MRI | Every 12 weeks | Every 8 to 9 weeks for first 24 weeks, then every 12 weeks† |

- PCWG3: Imaging interval decreased to 8-9 wks (instead of q12 wks) x 2 yrs; then q12 wks

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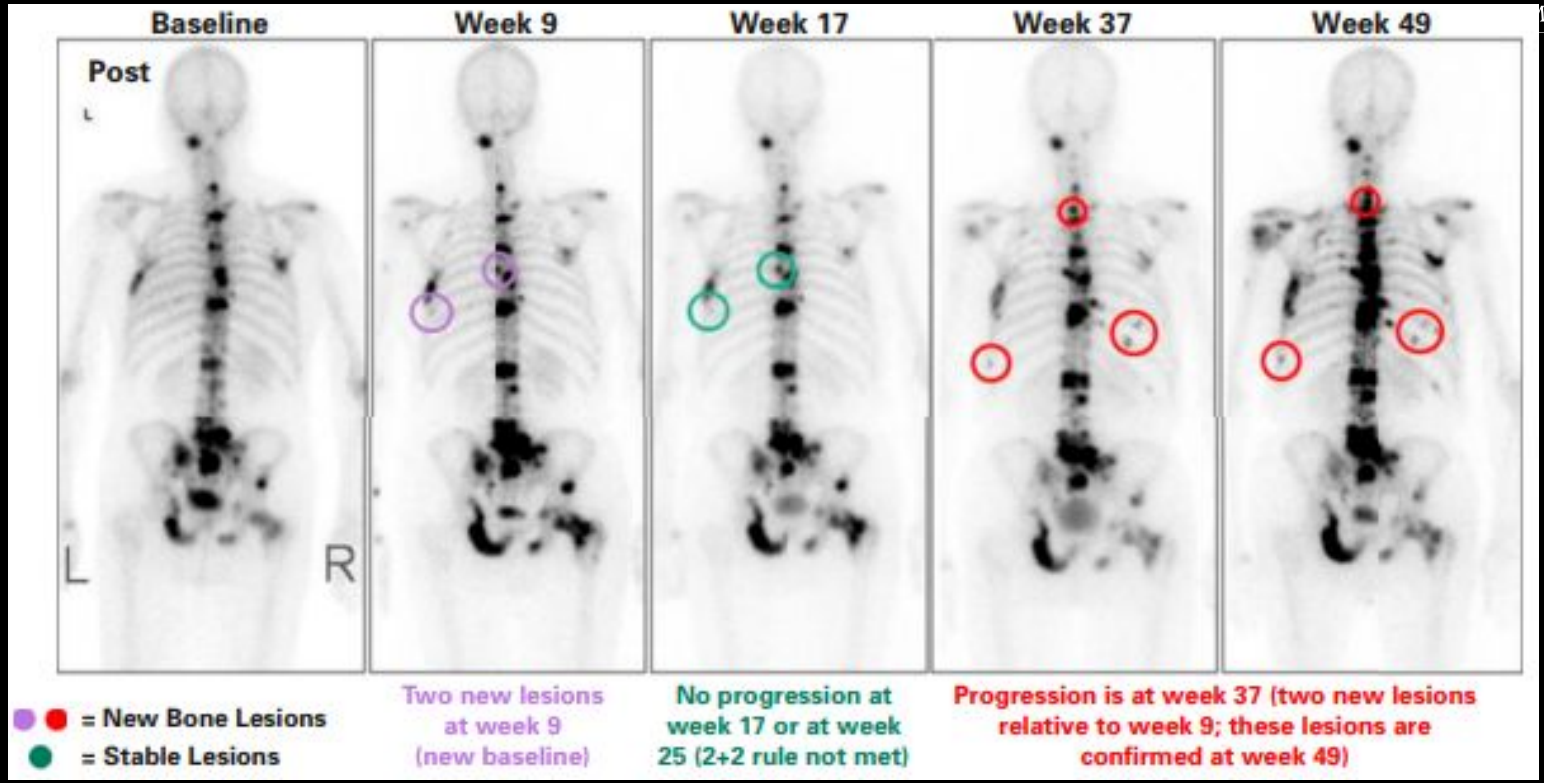
# Bone assessment




- First tx bone scan used as baseline
- Use of the 2+2 rule to distinguish flare from true progression (2 new lesions seen over 2 scans = 4 total new lesions)

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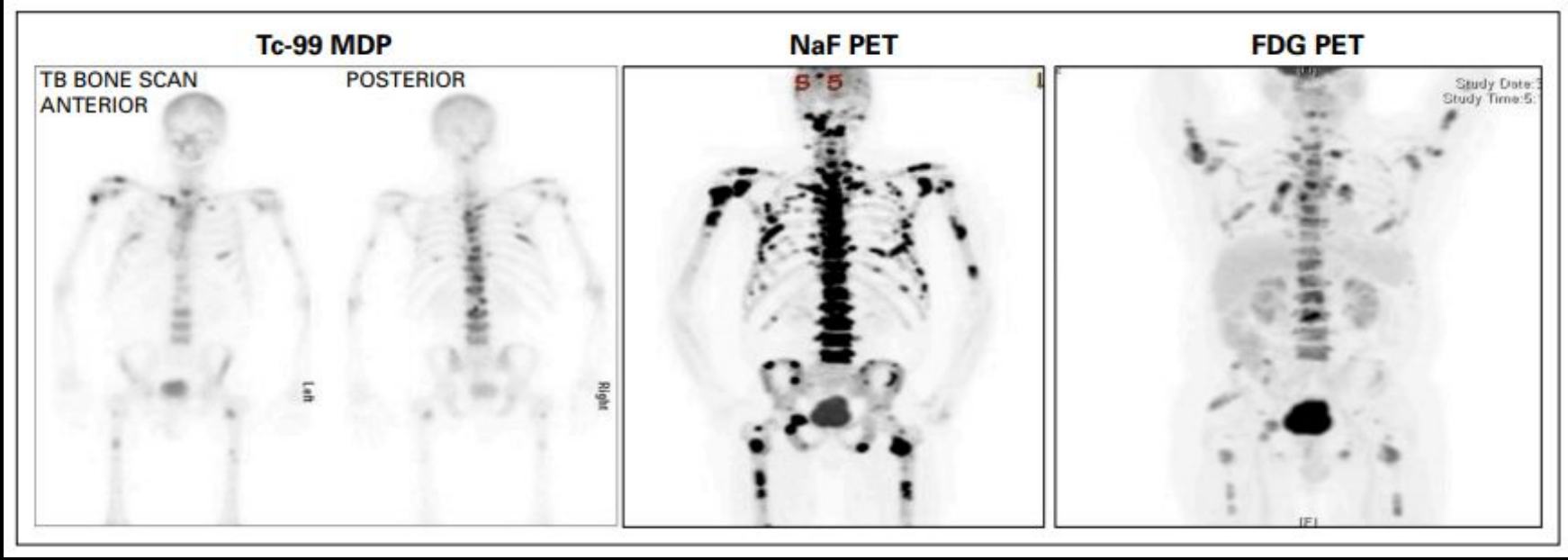
# Bone imaging




- Same patient with three different bone scan. Neither the target of the tracer nor the clarity of the image necessarily implies a superior biomarker, and each modality must be validated analytically and clinically.
- PCWG3 retains the use of Tc-99 MDP as the standard of imaging.
- Also encourages the use of the same bone scan imaging during follow up.

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B. Visceral metastasis are either ~~present or absent~~ Visceral mets sites must be specified
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