The Nuclear Medicine Day

September 15, 2016

Aseem Anand
Background – Why Bone Scan? (cont.)

*The evolving role of imaging in mCRPC*

- Recent developments:
  - PCWG2 criteria (Scher et al, JCO 2008) – recommendation to **overcome the flare** and variability in assessment
  - First drug approval by FDA in metastatic prostate cancer to use rPFS as co-primary endpoint (Kleutz et al CCR, 2013)
  - PCWG2 Validation towards surrogacy (Morris et al. JCO 2015)

Fig 3. Survival of patients with early bone scan progression (by 2 + 2 criteria) who failed to document progression (n = 166) versus those with documented progression on subsequent bone scan (n = 63). PD, progressive disease.
Methods: PCWG2 Form and Automated BSI platform
Need for quantitation and standardization of Bone Scan assessment

- Bone Scan Index (Imbriaco, Larson, et al. CCR 1998)
  - Bi-directional: Augments PCWG2
  - As a quantitative imaging parameter it can be incorporated into the multivariate prognostic or response biomarker models.
Bone Scan was Automated

Segmentation of Skeleton → Normalization → Hotspot Detection → Hotspot Classification → Bone Scan Index (BSI)

Video 1
Segmentation of Skeleton

Artificial Neural Network (ANN)

Input node → weights

Video 2
Hotspot classification

BSI: 5.8 (%) of total skeleton
Analytical Validation Studies for Qualification of BSI

Bone Scan Tc99-MDP

Bone Scan Index (BSI)

QC* Analysis

Pre-Analytical Study to standardize Bone Scan

- Different Camera
- Different Scanning time

Evaluating Analytical Performance

- BSI linearity/Accuracy
- BSI Precision
- BSI Inter-Observer variability

Clinical Qualification
Analytic Validation of the Automated Bone Scan Index as an Imaging Biomarker to Standardize Quantitative Changes in Bone Scans of Patients with Metastatic Prostate Cancer

Aseem Anand¹,², Michael J. Morris³, Reza Kaboteh³, Lena Báth⁴, May Sadik⁵, Peter Gjertsson⁵, Milan Lomsky⁵, Lars Edenbrandt¹,²,⁴, David Minarik⁵ and Anders Bjartell²,⁶

A Pre-Analytical Validation Study of Automated Bone Scan Index: Effect on Accuracy and Reproducibility due to the Procedural Variabilities in Bone Scan Image Acquisition.

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### TABLE 1

**Summary of Analytic Studies to Evaluate Performance Characteristics of Automated BSI as a Consistent Imaging Biomarker to Standardize Quantitative Analysis of Bone Scans**

<table>
<thead>
<tr>
<th>Analytic study</th>
<th>Objective</th>
<th>Design</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation study</td>
<td>Accuracy and precision</td>
<td>Simulation of bone scans with known phantom BSI as analytic standard</td>
<td>Measuring automated BSI against phantom BSI</td>
</tr>
<tr>
<td>Repeat bone scan study</td>
<td>Reproducibility</td>
<td>Metastatic patients with repeat bone scans</td>
<td>Measuring difference between 2 automated BSI interpretations</td>
</tr>
<tr>
<td>Follow-up bone scan study</td>
<td>Interobserver variability</td>
<td>Metastatic patients with 2 routine follow-up clinical bone scans</td>
<td>Measuring observer agreement in assessing automated BSI change</td>
</tr>
</tbody>
</table>

Result:
Accuracy & Precision

Linearity of the automated BSI simulated bone scans from 0.10 to 13.0 (N=50); Pearson’s r = 0.99 (p<0.0001)

Figure 3. (A) Simulated bone scan with known tumor burden corresponding to phantom BSI of 10.0. (B) Lesions detected and classified as metastatic by automated platform for BSI calculation are highlighted in red; arrows indicate simulated lesions at blind spot of automated BSI platform.
Result: Reproducibility

**FIGURE 2.** Bland–Altman plot to evaluate reproducibility of automated BSI interpretations from repeat bone scans of 35 metastatic patients. Mean BSI difference, 0.05 (solid horizontal line), with upper confidence limit of 0.30 and lower confidence limit of −0.25 (horizontal dotted lines).

Result: Inter-Osver Variability

**TABLE 4**
Pairwise Cohen κ Agreement Evaluating Interobserver Agreement Among 3 Independent Interpreters to Assess Changes in Bone Scans from 173 Patients with Metastatic Prostate Cancer

<table>
<thead>
<tr>
<th>Finding</th>
<th>Interpreter A vs. B</th>
<th>Interpreter A vs. C</th>
<th>Interpreter B vs. C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased burden</td>
<td>0.56</td>
<td>0.90</td>
<td>0.65</td>
</tr>
<tr>
<td>Two new lesions</td>
<td>0.62</td>
<td>0.81</td>
<td>0.55</td>
</tr>
<tr>
<td>Change in BSI</td>
<td>0.96</td>
<td>0.97</td>
<td>0.96</td>
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<thead>
<tr>
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<th>Objective</th>
<th>Design</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient studies: repeated bone scans in patients with skeletal metastasis</td>
<td>Effect on BSI, reproducibility</td>
<td>Grp1, repeated scan with same scanning speed and same camera as that of the first bone scan</td>
<td>Absolute value of the difference between the observed automated BSI values of the repeated bone scans</td>
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<td>Grp2, repeated scan with double (2x) scanning speed as that of the first bone scan</td>
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<td>Grp3, repeated scan with a γ-camera different from that of the first scan</td>
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<tr>
<td>Simulation studies: phantoms with predefined tumor burden (phantom-BSI)</td>
<td>Effect on BSI accuracy</td>
<td>Simulation with variable image counts</td>
<td>Absolute value of the difference between the observed automated BSI and the phantom-BSI</td>
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<td>Simulation with different γ-cameras</td>
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</tbody>
</table>
FIGURE 3. Respective automated BSI reads of simulated bone counts at 0.2, 0.5, 1.0, and 1.5 million image counts with predefined tumor burden corresponding to phantom-BSI of 3.0.

FIGURE 4. Box Plot representing the accuracy data under the respective image count Simulation.
FIGURE 1. Anterior and posterior (A/P) image count and associated automated BSI values in repeated bone scans of patients with same scanning speeds (Grp1) (A) and in repeated bone scans of patients with twice scanning speed of the scan (Grp2) (B). Doubling of scanning speed results in image count that is approximately half that of original scan. Lesions detected and classified as metastatic by automated platform, for BSI calculation, are highlighted in red.

FIGURE 2. Box plots representing reproducibility data in 3 predefined patient study groups.

75 patients; 25 in each grp
CONCLUSION

• BSI is a analytically reliable and consistent assessment of bone scan.
• **Garbage in – Garbage out:** The whole body bone scan procedure guidelines should be strictly followed to get clinically relevant results.
!!Bone Scan assessment needs a makeover!!

- Automatic lesion detection and classification
- Automatic tracking of old and new lesion and its location
- Automatic calculation of BSI
- Electronic Reports