Reviewer’s report

Title: Analysis of regional Bone Scan Index measurements for the survival of patients with prostate cancer

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Reviewer: Frederic Paycha

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1) Data accrued from national morbi-mortality registries are consistent over the concern of prevalence and prognosis impact of bone metastases in prostate cancer

a. Patients with metastatic prostate cancer abstracted from a large database, the Nationwide Inpatient Sample (1998–2010). Overall, 74,826 patients with metastatic prostate cancer were identified. The most common metastatic sites were bone (84%). When stratifying patients according to the site of metastases, only 19.4% of men with bone metastases had multiple non-bone sites involved (G Gandaglia, Prostate 2013).

b. Autopsy reports from Swiss registries retrieved 1,589 (8.2%) with prostate cancer. Hematogeneous metastases were present in 35% of 1,589 patients with prostate cancer, with most frequent involvement being bone (90%). Bone metastases were predominantly present in the spine (90%) (Metastatic Patterns of Prostate Cancer: An autopsy study of 1,589 patients. L Bubendorf. Hum Pathol 2000; 31:578-583)

c. Tumor registry data were collected between 1994-1996 on 11 primary tumor sites and 15 metastatic sites from 4399 patients. For prostate cancer, dominant metastatic site was bone (90%) and 86% of prostate primary tumors had only bone metastases (Kenneth R. Hess Metastatic Patterns in Adenocarcinoma Cancer 2006; 106: 1624–33).

2) Pattern of bone metastases on a planar bone whole body scan

The authors state that BSI algorithm© mimic experts pattern analysis in sorting out hot spots corresponding to bone metastases.

However, original criteria sets are never explicated in the manuscript. However, detailing scintigraphic patterns (on local, regional and general scales) is paramount to ascertain positive diagnosis of bone metastases and discarding differential diagnoses (some of them quoted by authors: fractures, osteoarthritis). Expliciting criteria sets is not only paramount for diagnostic accuracy but also for observers reproducibility. See for instance:

Paycha F, Girma A. Pattern-oriented approach in hybrid imaging (bisphosphonates-(99mTc) SPECT/CT and Fluoride-(18F) PET/CT) according to bone abnormality phenotype: The sclerotic/osteoblastic lesion and the


Another recent example in CT morphologic analysis of bone metastases can be found in Vargas et al. study. In this work, six local patterns were itemized: (a) osteoblastic dense, (b) osteoblastic ground glass, (c) osteoblastic mixed dense and ground glass, (d) miliary, (e) osteolytic, and (f) mixed osteolytic and osteoblastic (HA Vargas et al. Bone Metastases in Castration-Resistant Prostate Cancer: Associations between Morphologic CT Patterns, Glycolytic Activity, and Androgen Receptor Expression on PET and Overall Survival. Radiology 2014).

Without expliciting bone scan semiological (pattern) core, ANN and Cox models will stay grounded in shifting sands…

3) Discussion of regional pattern of bone metastases in prostate cancer

More than 50 years ago, Batson (Batson OV. The function of vertebral veins and their role in the spread of metastases. Arch Surg 1940; 112: 138-149) had suggested that a backward venous metastatic pathway from the prostate to the lower spine existed. This hypothesis was based on the observation of an unusually high prevalence of lower spine metastasis in prostate cancer and also on cadaver experiments. Taken together, these results strongly suggest that prostate cancer can follow 2 different hematogeneous metastatic pathways: a backward venous spread to the spine occurring early, and a dissemination through lung passage occurring later in the disease course.

The authors should incorporate this pathophysiological aspect in Discussion section.

Article from Singh at al, concluding that patients with <5 metastatic sites had significantly better survival rates than patients with >5 lesions, should be too mentioned in Discussion section (Singh D. Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Biol Phys 2004; 58 (1):3-10).

4) Suboptimal sensitivity of bone scan in prostate bone metastases

From autopsy data in 11 patients (188 axial skeletal specimens), MP Roudier evidenced only a 84% concordance between histologic and scintigraphic data (ie bone scan false negative rate = 13%). Limited sensitivity expressed by bone scan stem from intertrabecular metastases scarcely picked up by bone scans (Roudier MP, Vesselle H, True LD, Higano CS, Ott SM, King SH, Vessella RL. Bone histology at autopsy and matched bone scintigraphy findings in patients with hormone refractory prostate cancer: the effect of bisphosphonate therapy on bone scintigraphy results. Clin Exp Metastasis 2003; 20 (2): 171-80).

In keeping with this intertrabecular pathological picture, MRI has been shown to detect bone metastases: in 37.5% of patients with negative or inconclusive bone
scan, and one prospective study indicates sensitivities and specificities of 100 and 88% for MRI and 46 and 32% for bone scintigraphy (Lecouvet et al, 2007). Such less than optimal sensitivity of planar bone scan should be reminded and addressed in Discussion section, as authors somewhat addressed the specificity issue.

5) Planar bone scan vs bone SPECT-CT

As the authors stated, BSI foundations were published by Erdi et al in 1997; at this time, hybrid cameras were non-existent.

However, nowadays, hybrid cameras combining SPECT and spiral CT (SPECT-CT cameras) offer the opportunity to clarify around 90% findings classified as indeterminate on planar bone scintigraphy; such a figure emerged from ten or so published studies (JN Talbot, F Paycha, S Balogova. Diagnosis of bone metastasis: recent comparative studies of imaging modalities Q J Nucl Med Mol Imaging 2011; 55: 374-410).

SPECT-CT cameras are inexorably replacing older SPECT stand-alone cameras in Nuclear Medicine departments located in industrialized countries.

Did the authors compare planar BSI to “SPECT BSI”, which would/could prove more accurate to quantitatively assess bone metastatic burden?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests’