Author's response to reviews

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

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Version: 7 Date: 13 June 2014

Author's response to reviews: see over
Dear Editor, we are thankful for the excellent comments as well as the opportunity of resubmitting our work to your journal. We have tried to comply with each comment made by the reviewers. The next section contains a list of these comments along with our replies highlighted in gray.

Reviewer 1

Major #1: Method - study population
In this study, authors evaluated aBSI value using one bone scan imaging performed at “the last” for each patient. So, what means last? Does it mean last follow-up one? There are several situations for prostate cancer patients, for example, 1) at the diagnosis of prostate cancer, 2) during hormone therapy, 3) at the diagnosis of castration-resistance prostate cancer, 4) during chemotherapy, and 5) chemotherapy resistant. The prognosis is different between these situations. According to the mean follow-up period (mean 2.3 years), I think that most patients are at the stage of chemotherapy resistant. But more detailed explanation is required in this paper. If it is not possible, the author should consider this point as a limitation of this study and mention it in the limitation paragraph.

Answer:
Added in the method and discussion section.

Discretionary #1: Background
author writes “Recent works have....for prostate cancer patients”. According to author’s references, Kaboteh et al (Reference #6) have showed that aBSI changed could be a prognostic marker in addition to aBSI values. So I suggest something: “Recent works have shown that both total aBSI values and their changes are a prognostic indicator and ....for prostate cancer patients”. In addition, you had better adding the below reference in this sentence. Their work also demonstrated the usefulness of aBSI change in Pca. Mitsui Y et al. BJU Int. 2012 Dec;110(11 Pt B):E628-34. doi: 10.1111/j.1464-410X.2012.11355.x. Prediction of survival benefit using an automated bone scan index in patients with castration-resistant prostate cancer.
Answer:
A rewrite along the lines suggested by the reviewer has been done, as well as including the mentioned reference.

Discretionary #2: Discussion
author discussed that “Yamashita et al found that the localization of bone metastases in a........BSI change were alive after two years compared with only 18% of those with an increase in total BSI change (p=0.03) ” in the discussion. I think this line should include in the limitation or rewrite like this “Yamashita et al found that the presence of bone metastases outside the pelvis and the lumber spine is predictive of shorter survival time among the responders to the treatment. Thus, the localization of bone metastases may be a prognostic indicator if information of treatment response is also added. We have not considered therapy response in this study and can therefore not compare our results with theirs. Data obtaining therapy response are needed to clarify the true usefulness of regional BSI ."

Answer:
We have rewritten this specific paragraph according to the suggestions from the reviewer and a added a section to the limitations.

Minor #1: Background
you should exclude p-value (p=0.048) in background.

Answer:
The p-value has been removed from the background.

Minor #2: Discussion
“castration-resistant prostate cancer” should be used instead of “hormone-refractory prostate cancer”.

Answer:
“Hormone-resistant” has been changed to “castration-resistant”.

Reviewer 2

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

Answer:
We included prostate cancer patients undergoing bone scans with suspicious bone metastatic disease. Non-bone involvement has not been considered.

Comment 1b
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)

Answer:
We have collected our large patient population consecutively and present the distribution of their bone metastases without excluding specific subgroups.

Comment 1c
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).

Answer:
We included prostate cancer patients undergoing bone scans with suspicious bone metastatic disease. Non-bone involvement has not been considered.

Comment 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 explicited 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
Answer:
The method is used to classify hot spots into bone metastases or not is a machine learning method that is based on artificial neural networks (ANN). One property of the ANN is that it does not use any explicit set of criteria in the decision process. All the “knowledge” and “information” that the ANN is using is stored as a number of parameters (called weights). These parameters cannot be directly translated into a criteria set. During the classification process hotspot features are fed into the ANN which then computes a probability of the hotspot being metastatic, using the stored parameters. An advantage of using a blackbox method such as the ANN is that complex decisions can be made which would be difficult or cumbersome to state as explicit criteria.

However to provide more details about the decision system we have added a new reference in the manuscript showing the development and validation of our decision support system:

Computer-assisted interpretation of planar whole-body bone scans.

Comment 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).

Answer:
A comment has been added in the limitations section regarding Batson. A comparison with Singh has now been done and a paragraph of the results is included in the discussion.

Comment 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 bonescan, 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.

Answer:
We have added a comment on this issue in the limitations section.

Comment 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?
Answer:
We have added a comment on this issue in the limitations section.